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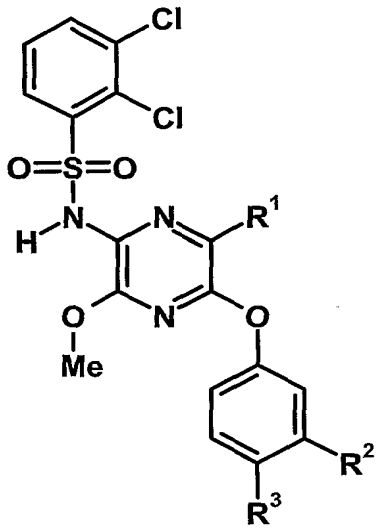
(54) Title: NOVEL N-PYRAZINIL-PHENYLSULFONAMIDE DERIVATIVES AS CHEMOKINE RECEPTOR MODULATORS FOR USE IN THE TREATMENT OF ASTHMA



(I)

(57) Abstract: The invention provides a compound of formula (I), wherein R^1, R^2 and R^3 are as defined in the specification, pharmaceutical compositions containing them, a process for preparing the pharmaceutical compositions, and their use in therapy.

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NOVEL N-PYRAZINYL-PHENYLSULFONAMIDE DERIVATIVES AS CHEMOKINE RECEPTOR MODULATORS FOR USE IN THE TREATMENT OF ASTHMA.

The present invention relates to sulphonamide compounds, processes and intermediates used in their preparation, pharmaceutical compositions containing them and their use in therapy.

Chemokines play an important role in immune and inflammatory responses in various diseases and disorders, including asthma and allergic diseases, as well as autoimmune pathologies such as rheumatoid arthritis and atherosclerosis. These small-secreted molecules are a growing superfamily of 8-14 kDa proteins characterised by a conserved four cysteine motif. At the present time, the chemokine superfamily comprises three groups exhibiting characteristic structural motifs, the Cys-X-Cys (C-X-C), Cys-Cys (C-C) and Cys-X_3-Cys (C-X_3-C) families. The C-X-C and C-C families have sequence similarity and are distinguished from one another on the basis of a single amino acid insertion between the NH-proximal pair of cysteine residues. The C-X_3-C family is distinguished from the other two families on the basis of having a triple amino acid insertion between the NH-proximal pair of cysteine residues.

The C-X-C chemokines include several potent chemoattractants and activators of neutrophils such as interleukin-8 (IL-8) and neutrophil-activating peptide 2 (NAP-2).

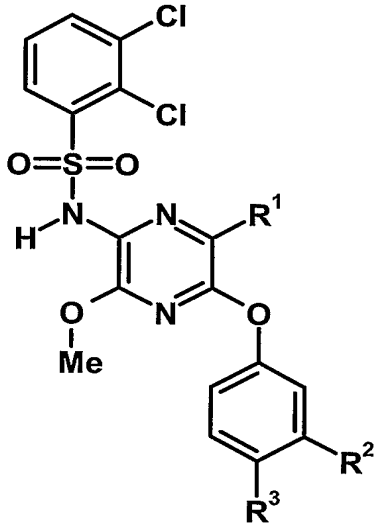
The C-C chemokines include potent chemoattractants of monocytes and lymphocytes but not neutrophils. Examples include human monocyte chemotactic proteins 1-3 (MCP-1, MCP-2 and MCP-3), RANTES (Regulated on Activation, Normal T Expressed and Secreted), eotaxin and the macrophage inflammatory proteins 1α and 1β (MIP-1α and MIP-1β), Thymus and Activation Regulated Chemokine (TARC, CCL17) and Macrophage Derived Chemokine (MDC, CCL22). The C-X_3-C chemokine (also known as fractalkine) is a potent chemoattractant and activator of microglia in the central nervous system (CNS) as well as of monocytes, T cells, NK cells and mast cells.

Studies have demonstrated that the actions of chemokines are mediated by subfamilies of G protein-coupled receptors, among which are the receptors designated CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR4, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10 and CCR11 (for the C-C family); CXCR1, CXCR2, CXCR3, CXCR4 and CXCR5 (for the C-X-C

family) and CX_3CR1 for the C-X_3-C family. These receptors represent good targets for drug development since agents which modulate these receptors would be useful in the treatment of disorders and diseases such as those mentioned above.

WO 03/051870 and WO 03/059893 disclose a series of sulphonamide compounds said to be useful for treating various diseases. It has now surprisingly been found that a narrow class of compounds generically disclosed in WO 03/059893 exhibit advantageous properties. For example, in addition to high potency, they also exhibit low plasma protein binding to human plasma, making the compounds efficacious for in vivo use.

The present invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof:

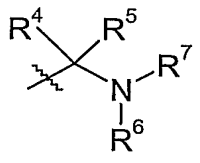


(I)

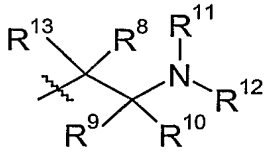
wherein

R^1 represents hydrogen, methyl, fluorine or chlorine;

one of R^2 and R^3 represents hydrogen or fluorine and the other of R^2 and R^3 represents a group of formula (IIA) or (IIB)



(IIA),



(IIB);

R^4 and R^5 each independently represent hydrogen, methyl or CH_2OH;

R^6 and R^7 each independently represent hydrogen, methyl, ethyl, or R^6 and R^7 together with the nitrogen atom to which they are attached form a 4-7 membered saturated heterocyclic ring;

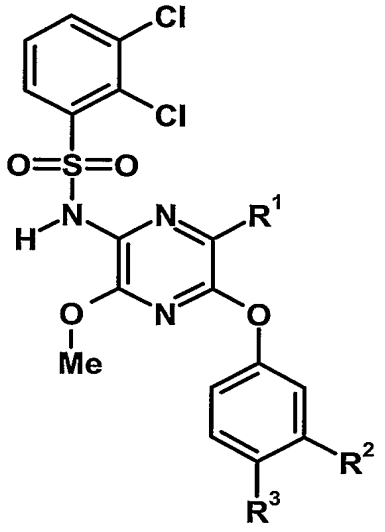
R^8 represents hydrogen or methyl;

R^{13} represents hydrogen, methyl or hydroxyl;

R^9 and R^{10} each independently represent hydrogen or methyl; and

R^{11} and R^{12} each independently represent hydrogen, methyl, ethyl, or R^{11} and R^{12} together with the nitrogen atom to which they are attached form a 4-7 membered saturated heterocyclic ring.

In one aspect the present invention provides a compound of formula

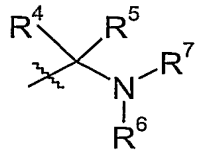


(I)

wherein

R^1 represents hydrogen, methyl or chlorine;

one of R^2 and R^3 represents hydrogen or fluorine and the other of R^2 and R^3 represents a group of formula (II)



(IIA);

R^4 and R^5 each independently represent hydrogen, methyl or CH_2OH; and

R^6 and R^7 each independently represent hydrogen, methyl, ethyl, or R^6 and R^7 together with the nitrogen atom to which they are attached form a 4-7 membered saturated heterocyclic ring.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and mixtures thereof including racemates. Tautomers and mixtures thereof also form an aspect of the present invention.

Suitable pharmaceutically acceptable salts of formula (I) include acid addition salts such as a hydrochloride, dihydrochloride, hydrobromide, phosphate, sulfate, acetate, diacetate, fumarate, maleate, tartrate, citrate, oxalate, methanesulfonate, benzenesulfonate or *p*-toluenesulfonate. Suitable salts also include metal salts, such as an alkali metal salt (for example a sodium or potassium salt) or an alkaline earth metal salt (for example magnesium or calcium). It will be understood that certain compounds of the present invention and pharmaceutically acceptable salts thereof may exist in solvated, for example hydrated, as well as unsolvated forms. It is to be understood that the present invention encompasses all such solvated forms.

In an embodiment of the invention, R^1 represents hydrogen or methyl.

In an embodiment of the invention, R^1 represents hydrogen or chlorine or fluorine.

In an embodiment of the invention, R^1 represents hydrogen.

In an embodiment of the invention, R^3 represents a group of formula (IIA) or (IIB) and R^2 represents hydrogen.

In an embodiment of the invention, R^2 represents a group of formula (IIA) or (IIB) and R^3 represents hydrogen.

In an embodiment of the invention, one of R^2 and R^3 represents hydrogen or fluorine and the other of R^2 and R^3 represents a group of formula (IIA).

In an embodiment of the invention, R^3 represents a group of formula (IIA) and R^2 represents hydrogen.

In an embodiment of the invention, R^2 represents a group of formula (IIA) and R^3 represents hydrogen.

In an embodiment of the invention, R^4 and R^5 each independently represent hydrogen or methyl.

In an embodiment of the invention, one of R^4 and R^5 represents methyl and the other of R^4 and R^5 represents hydrogen.

In an embodiment of the invention, one of R^4 and R^5 represents CH_2OH and the other of R^4 and R^5 represents hydrogen.

In an embodiment of the invention, R^6 and R^7 each independently represent hydrogen or methyl.

In an embodiment of the invention, R^6 and R^7 each independently represent hydrogen.

When R^6 and R^7 together with the nitrogen atom to which they are attached form a 4-7 membered saturated heterocyclic ring, examples of saturated heterocyclic rings include azetidine, pyrrolidine and piperidine. In an embodiment of the invention, R^6 and R^7 together with the nitrogen atom to which they are attached form a piperidine ring.

In one aspect the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^1 represents hydrogen, R^2 represents hydrogen and R^3 represents a group of formula (IIA) wherein R^4 and R^5 each independently represent hydrogen or methyl, and R^6 and R^7 each independently represent hydrogen.

In a further aspect the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^1 represents hydrogen, R^2 represents hydrogen and R^3 represents a group of formula (IIA) wherein R^4 and R^5 each independently represent hydrogen or CH_2OH, and R^6 and R^7 each independently represent hydrogen.

In an embodiment of the invention, one of R^2 and R^3 represents hydrogen or fluorine and the other of R^2 and R^3 represents a group of formula (IIB).

In an embodiment of the invention, R^3 represents a group of formula (IIB) and R^2 represents hydrogen.

In an embodiment of the invention, R^2 represents a group of formula (IIB) and R^3 represents hydrogen.

In an embodiment of the invention, R^8 represents hydrogen.

In an embodiment of the invention, R^{13} represents hydroxyl;

In an embodiment of the invention, R^9 and R^{10} each represent hydrogen.

In an embodiment of the invention, R^{11} and R^{12} each independently represent hydrogen or methyl.

In an embodiment of the invention, R^{11} and R^{12} each independently represent hydrogen.

When R^{11} and R^{12} together with the nitrogen atom to which they are attached form a 4-7 membered saturated heterocyclic ring, examples of saturated heterocyclic rings include azetidine, pyrrolidine and piperidine. In an embodiment of the invention, R^{11} and R^{12} together with the nitrogen atom to which they are attached form a piperidine ring.

In one aspect the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof, wherein R^1 represents hydrogen, R^2 represents hydrogen and R^3 represents a group of formula (IIB), wherein R^8 represents hydrogen, R^{13} represents hydroxyl, R^9 and R^{10} each independently represent hydrogen and R^{11} and R^{12} each independently represent hydrogen or methyl.

In an embodiment of the present invention the compound of formula (I) is selected from:

N-{5-[4-(Aminomethyl)phenoxy]-3-methoxypyrazinyl}-2,3-dichlorobenzenesulphonamide,

N-(5-{4-[(*R*)-1-Aminoethyl]phenoxy}-3-methoxypyrazinyl)-2,3-dichlorobenzenesulphonamide,

N-(5-{4-[(*R*)-1-Aminoethyl]phenoxy}-3-methoxy-6-methylpyrazinyl)-2,3-dichlorobenzenesulphonamide,

N-{5-[3-((S)-1-Aminoethyl)phenoxy]-3-methoxypyrazinyl}-2,3-dichlorobenzenesulphonamide,

N-{5-[3-((R)-1-Aminoethyl)phenoxy]-3-methoxypyrazinyl}-2,3-dichlorobenzenesulphonamide,

N-{5-[3-((S)-1-Aminoethyl)phenoxy]-3-methoxy-6-methylpyrazinyl}-2,3-dichlorobenzenesulphonamide,

N-(5-{4-[(*S*)-1-Aminoethyl]phenoxy}-3-methoxypyrazinyl)-2,3-dichlorobenzenesulphonamide,

2,3-Dichloro-*N*-(3-methoxy-5-{4-[(1S)-1-(methylamino)ethyl]phenoxy}pyrazinyl)benzenesulphonamide,

N-(5-{4-[(1*S*)-1-Aminoethyl]phenoxy}-3-methoxy-6-methylpyrazinyl)-2,3-dichlorobenzenesulphonamide,

N-(5-{4-[(1*S*)-1-Amino-2-hydroxyethyl]phenoxy}-3-methoxypyrazinyl)-2,3-dichlorobenzenesulphonamide,

N-{5-[4-(Aminomethyl)-3-fluorophenoxy]-3-methoxypyrazinyl}-2,3-dichlorobenzenesulphonamide,

2,3-Dichloro-*N*-(3-methoxy-5-{4-[(1*R*)-1-(methylamino)ethyl]phenoxy}pyrazinyl)benzenesulphonamide,

2,3-Dichloro-*N*-{3-methoxy-5-[3-(1-piperidinylmethyl)phenoxy]pyrazinyl}benzenesulphonamide,

N-[5-[4-[(1*S*)-1-Amino-2-hydroxyethyl]phenoxy]-3-methoxy-6-methylpyrazinyl]-2,3-dichlorobenzenesulphonamide,

N-[5-[4-[(1*R*)-1-Amino-2-hydroxyethyl]phenoxy]-3-methoxypyrazinyl]-2,3-dichlorobenzenesulphonamide,

2,3-Dichloro-*N*-[6-chloro-3-methoxy-5-[4-[(1*R*)-1-(methylamino)ethyl]phenoxy]pyrazinyl]benzenesulfonamide,

N-[5-[4-(1-Amino-1-methylethyl)phenoxy]-3-methoxypyrazinyl]-2,3-dichlorobenzenesulphonamide

2,3-Dichloro-*N*-[3-methoxy-6-methyl-5-[4-[(1*R*)-1-(methylamino)ethyl]phenoxy]pyrazin-2-yl]-benzenesulphonamide

2,3-Dichloro-*N*-(3-methoxy-5-{4-[(methylamino)methyl]phenoxy}pyrazin-2-yl)benzenesulfonamide

N-[5-[4-[(1*S*)-1-Amino-2-hydroxyethyl]phenoxy]-6-chloro-3-methoxypyrazinyl]-2,3-dichlorobenzenesulphonamide

N-(5-{4-[(1*R*)-1-Aminoethyl]phenoxy}-6-fluoro-3-methoxypyrazin-2-yl)-2,3-dichlorobenzenesulfonamide

N-[5-[4-[(1*S*)-1-Amino-2-hydroxyethyl]phenoxy]-6-fluoro-3-methoxypyrazin-2-yl]-2,3-dichlorobenzenesulphonamide

2,3-Dichloro-*N*-[5-[4-[(1*R*)-2-hydroxy-1-(methylamino)ethyl]phenoxy]-3-methoxypyrazin-2-yl]benzenesulphonamide

N-[5-[4-[(1*R*)-1-Amino-2-hydroxyethyl]phenoxy]-3-methoxy-6-methylpyrazin-2-yl]-2,3-dichlorobenzenesulphonamide

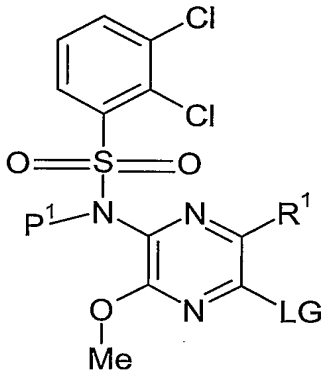
N-(5-{4-[(1*S*)-1-aminoethyl]phenoxy}-6-fluoro-3-methoxypyrazin-2-yl)-2,3-dichlorobenzenesulfonamide

N-{5-[4-(2-amino-1-hydroxyethyl)phenoxy]-3-methoxypyrazin-2-yl}-2,3-dichlorobenzenesulfonamide

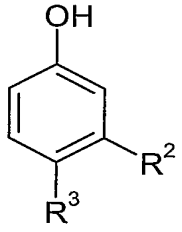
or a pharmaceutically acceptable salt thereof.

According to the present invention there is also provided a process for the preparation of a compound of formula (I), or a pharmaceutically acceptable salt thereof, which comprises:

(a) reacting a compound of formula (III) wherein R^1 is as defined in formula (I), LG is a leaving group (e.g. a halogen or O-triflate) and P^1 is a suitable protecting group (e.g. para-methoxybenzyl or 2-trimethylsilanylethoxymethyl) with a compound of formula (IV) wherein R^2 and R^3 are as defined in formula (I),

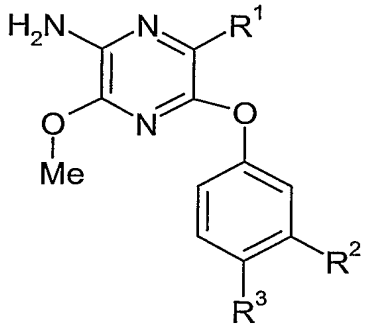


(III),



(IV); or

(b) reacting a compound of formula (V), wherein R^1, R^2 and R^3 are as defined in formula (I) with 2,3-dichlorobenzenesulfonyl chloride,



(V)

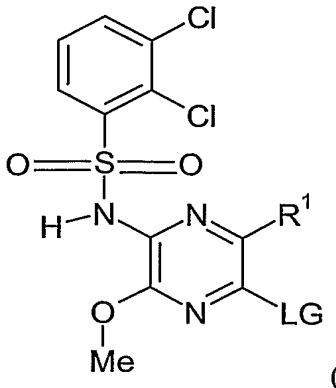
and optionally after (a) or (b) carrying out one or more of the following:

- removing any protecting groups
- converting the compound to a further compound of the invention
- forming a pharmaceutically acceptable salt of the compound.

In process (a) the reaction may conveniently be carried out in a suitable solvent such as DMF (N,N-dimethylformamide), NMP (N-methyl-2-pyrrolidinone) or acetonitrile, at a temperature in the range of 20 to 50 °C, under the influence of basic reagents such as K_2CO_3 or Cs_2CO_3 or NaH.

In process (b) the reaction may conveniently be carried out in a suitable solvent such 1,2-dimethoxyethane or tetrahydrofuran, at a temperature in the range of 0 to 50 °C, under the influence of a base such as NaH or potassium tert-butoxide.

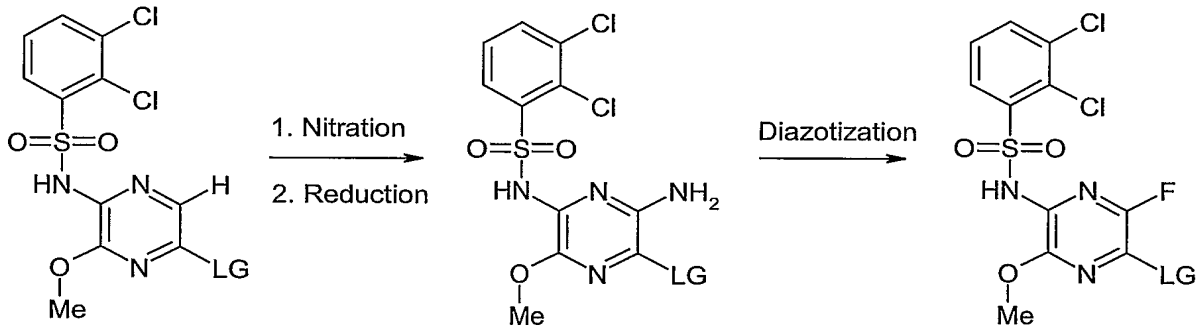
Compounds of formula (III) may be prepared by protecting a compound of formula (VI) with suitable protecting group P^1. For example, when P^1 is para-methoxybenzyl compounds of formula (III) may be prepared by treating (VI) with para methoxybenzylchloride in the presence of a suitable base such as triethylamine, N-ethyl-N-isopropylpropan-2-amine, sodium carbonate or sodium bicarbonate in a solvent such as acetonitrile or N-methyl-2-pyrrolidinone at room temperature (e.g. 20 to 30 °C) to 90°C. Alternatively, when P^1 is 2-trimethylsilanyl-ethoxymethyl compounds of formula (III) may be prepared by treating (VI) with [2-(chloromethoxy)ethyl](trimethyl)silane and a suitable base such as triethylamine or N-ethyl-N-isopropylpropan-2-amine in a suitable solvent such as dichloromethane at a temperature in the range of 0 to 30 °C. Protecting group P^1 may later be removed using acidic conditions such as 4N HCl in dioxan or trifluoroacetic acid in dichloromethane at room temperature.



(VI)

Compounds of formula (VI) may be prepared by methods according or analogous to those described in WO03/059893. Additionally, compounds of formula (VI) wherein R^1 is fluorine may be prepared from compounds of formula (VI) wherein R^1 is hydrogen by a process as depicted in reaction Scheme 1. In Scheme 1 a compound of formula (VI) wherein R^1 is hydrogen is subjected to sequential nitration and reduction to yield a compound of formula (VIa). The nitration may be carried out, for example, by using nitronium tetrafluoroborate in a suitable solvent such as acetonitrile at a suitable temperature such as ambient temperature (e.g. 20 °C). The reduction may be carried out, for example, by hydrogenation at a suitable pressure such as 1 bar using a suitable catalyst such as palladium on charcoal in a suitable solvent such as ethyl acetate/acetic acid. Compounds of formula (VIa) may then be subject to diazotization/fluorination conditions, for example using sodium nitrite and hydrogen fluoride-pyridine at a suitable temperature such as 0 to -20 °C, to give compounds of formula (VI).

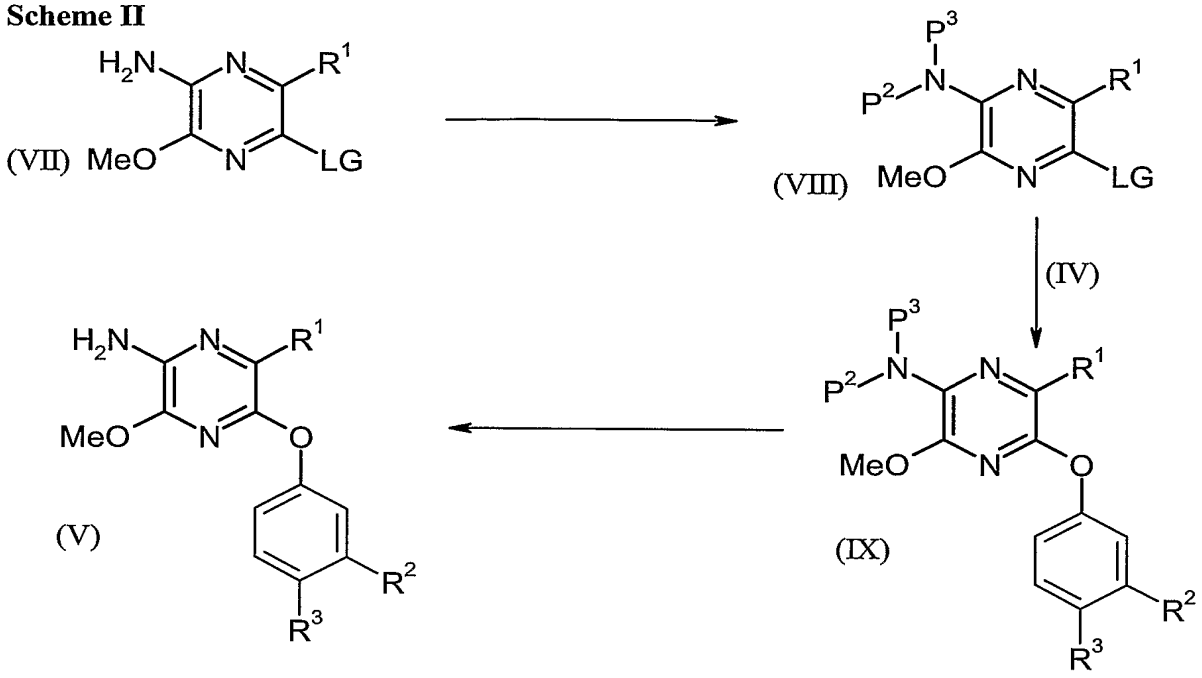
Scheme I



Compounds of formula (IV) can be prepared using methods according or analogous to those described in the literature.

Compounds of formula (V) can, for example, be prepared from a compound of formula (VII) as depicted in reaction Scheme II, wherein R^1, R^2 and R^3 are as defined in formula (I) and LG is a leaving group (e.g. a halogen or O-triflate).

Scheme II



As depicted in Scheme II, the amine group in (VII) is protected with a suitable protecting group such as a phthalimide (for example by treating with phthalic anhydride in a suitable solvent such as acetic acid and heating at 80-110 °C) or a 2,5-dimethylpyrrole (for example by treating with hexane-2,5-dione, in a suitable solvent such as toluene in the presence of an acid such as p-toluenesulphonic acid and heating at 80-110 °C) to give a compound of formula (VIII), wherein NP^2P^3 represents the protected amine group.

Compound (VIII) is then reacted with a compound of formula (IV) as described in process (a) to give compound (IX). The reaction of compounds (VIII) and (IV) may conveniently be carried out in a suitable solvent such as DMF (N,N-dimethylformamide), NMP (N-methyl-2-pyrrolidinone) or acetonitrile at a temperature in the range of 20 to 50 °C under the influence of a basic reagent such as K_2CO_3 or Cs_2CO_3 or NaH.

The amine protecting group is then removed from compound (IX) to give (V). For example, when the amine group is protected as a phthalimide it may be removed by treating with hydrazine hydrate in a suitable solvent such as ethanol and heating at reflux. Alternatively, when the amine group is protected as a 2,5-dimethylpyrrole it may be removed by treating with hydroxylamine hydrochloride, water and triethylamine in a suitable solvent such as ethanol or iso-propanol and heating at reflux.

It will be appreciated by those skilled in the art that in the processes of the present invention certain functional groups such as hydroxyl, carboxyl or amino groups in the starting reagents or intermediate compounds may need to be protected by protecting groups. Thus, the preparation of the compounds of formula (I) may involve at a certain stage the addition/removal of one or more protecting groups. The protection and deprotection of functional groups is described in 'Protective Groups in Organic Synthesis', 2nd edition, T.W. Greene and P.G.M. Wuts, Wiley-Interscience (1991) and 'Protecting Groups', P.J. Kocienski, Georg Thieme Verlag (1994).

The compounds of the invention, or pharmaceutically acceptable salts thereof, have activity as pharmaceuticals, in particular as modulators of chemokine receptor (especially CCR4) activity. Diseases and conditions which may be treated with the compounds include:

1. *respiratory tract*: obstructive diseases of the airways including: asthma, including bronchial, allergic, intrinsic, extrinsic, exercise-induced, drug-induced (including aspirin and NSAID-induced) and dust-induced asthma, both intermittent and persistent and of all severities, and other causes of airway hyper-responsiveness; chronic obstructive pulmonary disease (COPD); bronchitis, including infectious and eosinophilic bronchitis; emphysema; bronchiectasis; cystic fibrosis; sarcoidosis; farmer's lung and related diseases; hypersensitivity pneumonitis; lung fibrosis, including cryptogenic fibrosing alveolitis, idiopathic interstitial pneumonias, fibrosis complicating anti-neoplastic therapy and chronic infection, including tuberculosis and aspergillosis and other fungal infections; complications of lung transplantation; vasculitic and thrombotic disorders of the lung vasculature, and pulmonary hypertension; antitussive activity including treatment of chronic cough associated with inflammatory and secretory conditions of the airways, and iatrogenic cough; acute and chronic rhinitis including rhinitis medicamentosa, and vasomotor rhinitis; perennial and seasonal allergic rhinitis including rhinitis nervosa (hay fever); nasal polyposis; acute viral infection including the common cold, and infection due to respiratory syncytial virus, influenza, coronavirus (including SARS) and adenovirus;

2. *bone and joints*: arthritides associated with or including osteoarthritis/osteoarthrosis, both primary and secondary to, for example, congenital hip dysplasia; cervical and lumbar

spondylitis, and low back and neck pain; rheumatoid arthritis and Still's disease; seronegative spondyloarthropathies including ankylosing spondylitis, psoriatic arthritis, reactive arthritis and undifferentiated spondarthropathy; septic arthritis and other infection-related arthopathies and bone disorders such as tuberculosis, including Potts' disease and Poncet's syndrome; acute and chronic crystal-induced synovitis including urate gout, calcium pyrophosphate deposition disease, and calcium apatite related tendon, bursal and synovial inflammation; Behcet's disease; primary and secondary Sjogren's syndrome; systemic sclerosis and limited scleroderma; systemic lupus erythematosus, mixed connective tissue disease, and undifferentiated connective tissue disease; inflammatory myopathies including dermatomyositits and polymyositis; polymalgia rheumatica; juvenile arthritis including idiopathic inflammatory arthritides of whatever joint distribution and associated syndromes, and rheumatic fever and its systemic complications; vasculitides including giant cell arteritis, Takayasu's arteritis, Churg-Strauss syndrome, polyarteritis nodosa, microscopic polyarteritis, and vasculitides associated with viral infection, hypersensitivity reactions, cryoglobulins, and paraproteins; low back pain; Familial Mediterranean fever, Muckle-Wells syndrome, and Familial Hibernian Fever, Kikuchi disease; drug-induced arthalgias, tendonititides, and myopathies;

3. *pain and connective tissue remodelling of musculoskeletal disorders due to injury [for example sports injury] or disease*: arthitides (for example rheumatoid arthritis, osteoarthritis, gout or crystal arthropathy), other joint disease (such as intervertebral disc degeneration or temporomandibular joint degeneration), bone remodelling disease (such as osteoporosis, Paget's disease or osteonecrosis), polychondritits, scleroderma, mixed connective tissue disorder, spondyloarthropathies or periodontal disease (such as periodontitis);

4. *skin*: psoriasis, atopic dermatitis, contact dermatitis or other eczematous dermatoses, and delayed-type hypersensitivity reactions; phyto- and photodermatitis; seborrhoeic dermatitis, dermatitis herpetiformis, lichen planus, lichen sclerosus et atrophica, pyoderma gangrenosum, skin sarcoid, discoid lupus erythematosus, pemphigus, pemphigoid, epidermolysis bullosa, urticaria, angioedema, vasculitides, toxic erythemas, cutaneous eosinophilias, alopecia areata, male-pattern baldness, Sweet's syndrome, Weber-Christian

syndrome, erythema multiforme; cellulitis, both infective and non-infective; panniculitis;cutaneous lymphomas, non-melanoma skin cancer and other dysplastic lesions; drug-induced disorders including fixed drug eruptions;

5. *eyes*: blepharitis; conjunctivitis, including perennial and vernal allergic conjunctivitis; iritis; anterior and posterior uveitis; choroiditis; autoimmune; degenerative or inflammatory disorders affecting the retina; ophthalmitis including sympathetic ophthalmitis; sarcoidosis; infections including viral , fungal, and bacterial;

6. *gastrointestinal tract*: glossitis, gingivitis, periodontitis; oesophagitis, including reflux; eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, colitis including ulcerative colitis, proctitis, pruritis ani; coeliac disease, irritable bowel syndrome, and food-related allergies which may have effects remote from the gut (for example migraine, rhinitis or eczema);

7. *abdominal*: hepatitis, including autoimmune, alcoholic and viral; fibrosis and cirrhosis of the liver; cholecystitis; pancreatitis, both acute and chronic;

8. *genitourinary*: nephritis including interstitial and glomerulonephritis; nephrotic syndrome; cystitis including acute and chronic (interstitial) cystitis and Hunner's ulcer; acute and chronic urethritis, prostatitis, epididymitis, oophoritis and salpingitis; vulvo-vaginitis; Peyronie's disease; erectile dysfunction (both male and female);

9. *allograft rejection*: acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea or following blood transfusion; or chronic graft versus host disease;

10. *CNS*: Alzheimer's disease and other dementing disorders including CJD and nvCJD; amyloidosis; multiple sclerosis and other demyelinating syndromes; cerebral atherosclerosis and vasculitis; temporal arteritis; myasthenia gravis; acute and chronic pain (acute, intermittent or persistent, whether of central or peripheral origin) including visceral pain, headache, migraine, trigeminal neuralgia, atypical facial pain, joint and bone pain, pain arising from cancer and tumor invasion, neuropathic pain syndromes including diabetic, post-herpetic, and HIV-associated neuropathies; neurosarcoidosis; central and peripheral nervous system complications of malignant, infectious or autoimmune processes;

11. other auto-immune and allergic disorders including Hashimoto's thyroiditis, Graves' disease, Addison's disease, diabetes mellitus, idiopathic thrombocytopaenic purpura, eosinophilic fasciitis, hyper-IgE syndrome, antiphospholipid syndrome;

12. other disorders with an inflammatory or immunological component; including acquired immune deficiency syndrome (AIDS), leprosy, Sezary syndrome, and paraneoplastic syndromes;

13. *cardiovascular*: atherosclerosis, affecting the coronary and peripheral circulation; pericarditis; myocarditis , inflammatory and auto-immune cardiomyopathies including myocardial sarcoid; ischaemic reperfusion injuries; endocarditis, valvulitis, and aortitis including infective (for example syphilitic); vasculitides; disorders of the proximal and peripheral veins including phlebitis and thrombosis, including deep vein thrombosis and complications of varicose veins;

14. *oncology*: treatment of common cancers including prostate, breast, lung, ovarian, pancreatic, bowel and colon, stomach, skin and brain tumors and malignancies affecting the bone marrow (including the leukaemias) and lymphoproliferative systems, such as Hodgkin's and non-Hodgkin's lymphoma; including the prevention and treatment of metastatic disease and tumour recurrences, and paraneoplastic syndromes; and,

15. *gastrointestinal tract*: Coeliac disease, proctitis, eosinopilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, microscopic colitis, indeterminant colitis, irritable bowel disorder, irritable bowel syndrome, non-inflammatory diarrhea, food-related allergies which have effects remote from the gut, e.g., migraine, rhinitis and eczema.

Accordingly, the present invention further provides a compound of formula (I), or a pharmaceutically-acceptable salt thereof, as hereinbefore defined for use in therapy.

The compounds of the present invention may be used to treat diseases by modulating activity of a CC chemokine receptor subfamily, in particular, by modulating activity of the CCR4 receptor. Particular conditions which can be treated with the compound of the invention are asthma, rhinitis and inflammatory skin disorders, diseases in which there are raised TARC, MDC or CCR4 levels.

In a further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In a still further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined in the manufacture of a medicament for the treatment of human diseases or conditions in which modulation of chemokine receptor activity, particularly CCR4 activity, is beneficial.

In a still further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined in the manufacture of a medicament for the treatment of asthma.

In a still further aspect, the present invention provides the use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined in the manufacture of a medicament for the treatment of chronic obstructive pulmonary disease,

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

The invention still further provides a method of treating a chemokine mediated disease wherein the chemokine binds to a chemokine (especially CCR4) receptor, which comprises administering to a patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined.

The invention also provides a method of treating a respiratory disease, such as athma and rhinitis, especially asthma, in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the compound employed, the mode of administration, the treatment desired and the disorder indicated.

The compound of formula (I) and pharmaceutically acceptable salts thereof may be used on their own but will generally be administered in the form of a pharmaceutical composition in which the formula (I) compound/salt (active ingredient) is in association

with a pharmaceutically acceptable adjuvant, diluent or carrier. Depending on the mode of administration, the pharmaceutical composition will preferably comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The present invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined, in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing a compound of formula (I), or a pharmaceutically acceptable salt thereof, as hereinbefore defined, with a pharmaceutically acceptable adjuvant, diluent or carrier.

The pharmaceutical compositions may be administered topically (e.g. to the lung and/or airways or to the skin) in the form of solutions, suspensions, heptafluoroalkane aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules, or by parenteral administration in the form of solutions or suspensions, or by subcutaneous administration or by rectal administration in the form of suppositories or transdermally. Conveniently the compound of the invention is administered orally.

The invention further relates to combination therapies wherein a compound of the invention, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition or formulation comprising a compound of the invention, is administered concurrently or sequentially or as a combined preparation with another therapeutic agent or agents, for the treatment of one or more of the conditions listed.

In particular, for the treatment of the inflammatory diseases such as (but not restricted to) rheumatoid arthritis, osteoarthritis, asthma, allergic rhinitis, chronic obstructive pulmonary disease (COPD), psoriasis, and inflammatory bowel disease, the compounds of the invention may be combined with agents listed below.

Non-steroidal anti-inflammatory agents (hereinafter NSAIDs) including non-selective cyclo-oxygenase COX-1 / COX-2 inhibitors whether applied topically or systemically

(such as piroxicam, diclofenac, propionic acids such as naproxen, flurbiprofen, fenoprofen, ketoprofen and ibuprofen, fenamates such as mefenamic acid, indomethacin, sulindac, azapropazone, pyrazolones such as phenylbutazone, salicylates such as aspirin); selective COX-2 inhibitors (such as meloxicam, celecoxib, rofecoxib, valdecoxib, lumarocoxib, parecoxib and etoricoxib); cyclo-oxygenase inhibiting nitric oxide donors (CINODs); glucocorticosteroids (whether administered by topical, oral, intramuscular, intravenous, or intra-articular routes); methotrexate; leflunomide; hydroxychloroquine; d-penicillamine; auranofin or other parenteral or oral gold preparations; analgesics; diacerein; intra-articular therapies such as hyaluronic acid derivatives; and nutritional supplements such as glucosamine.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, together with a cytokine or agonist or antagonist of cytokine function, (including agents which act on cytokine signalling pathways such as modulators of the SOCS system) including alpha-, beta-, and gamma-interferons; insulin-like growth factor type I (IGF-1); interleukins (IL) including IL1 to 17, and interleukin antagonists or inhibitors such as anakinra; tumour necrosis factor alpha (TNF-α) inhibitors such as anti-TNF monoclonal antibodies (for example infliximab; adalimumab, and CDP-870) and TNF receptor antagonists including immunoglobulin molecules (such as etanercept) and low-molecular-weight agents such as pentoxyfylline.

In addition the invention relates to a combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, with a monoclonal antibody targeting B-Lymphocytes (such as CD20 (rituximab), MRA-aIL16R and T-Lymphocytes, CTLA4-Ig, HuMax Il-15).

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, with a modulator of chemokine receptor function such as an antagonist of CCR1, CCR2, CCR2A, CCR2B, CCR3, CCR5, CCR6, CCR7, CCR8, CCR9, CCR10 and CCR11 (for the C-C family); CXCR1, CXCR2, CXCR3, CXCR4 and CXCR5 (for the C-X-C family) and CX_3CR1 for the $C\text{-}X_3\text{-}C$ family.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, with an inhibitor of matrix metalloprotease (MMPs), i.e., the stromelysins, the collagenases, and the gelatinases, as

well as aggrecanase; especially collagenase-1 (MMP-1), collagenase-2 (MMP-8), collagenase-3 (MMP-13), stromelysin-1 (MMP-3), stromelysin-2 (MMP-10), and stromelysin-3 (MMP-11) and MMP-9 and MMP-12, including agents such as doxycycline.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a leukotriene biosynthesis inhibitor, 5-lipoxygenase (5-LO) inhibitor or 5-lipoxygenase activating protein (FLAP) antagonist such as; zileuton; ABT-761; fenleuton; tepoxalin; Abbott-79175; Abbott-85761; a N-(5-substituted)-thiophene-2-alkylsulfonamide; 2,6-di-tert-butylphenolhydrazones; a methoxytetrahydropyrans such as Zeneca ZD-2138; the compound SB-210661; a pyridinyl-substituted 2-cyanonaphthalene compound such as L-739,010; a 2-cyanoquinoline compound such as L-746,530; or an indole or quinoline compound such as MK-591, MK-886, and BAY x 1005.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a receptor antagonist for leukotrienes (LT) B4, LTC4, LTD4, and LTE4 selected from the group consisting of the phenothiazin-3-1s such as L-651,392; amidino compounds such as CGS-25019c; benzoxalamines such as ontazolast; benzenecarboximidamides such as BIIL 284/260; and compounds such as zafirlukast, ablukast, montelukast, pranlukast, verlukast (MK-679), RG-12525, Ro-245913, iralukast (CGP 45715A), and BAY x 7195.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a phosphodiesterase (PDE) inhibitor such as a methylxanthanine including theophylline and aminophylline; a selective PDE isoenzyme inhibitor including a PDE4 inhibitor an inhibitor of the isoform PDE4D, or an inhibitor of PDE5.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a histamine type 1 receptor antagonist such as cetirizine, loratadine, desloratadine, fexofenadine, acrivastine, terfenadine, astemizole, azelastine, levocabastine, chlorpheniramine, promethazine, cyclizine, or mizolastine; applied orally, topically or parenterally.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a proton pump inhibitor (such as omeprazole) or a gastroprotective histamine type 2 receptor antagonist.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and an antagonist of the histamine type 4 receptor.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and an alpha-1/alpha-2 adrenoceptor agonist vasoconstrictor sympathomimetic agent, such as propylhexedrine, phenylephrine, phenylpropanolamine, ephedrine, pseudoephedrine, naphazoline hydrochloride, oxymetazoline hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride, tramazoline hydrochloride or ethylnorepinephrine hydrochloride.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and an anticholinergic agents including muscarinic receptor (M1, M2, and M3) antagonist such as atropine, hyoscine, glycopyrrrolate, ipratropium bromide, tiotropium bromide, oxitropium bromide, pirenzepine or telenzepine.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a beta-adrenoceptor agonist (including beta receptor subtypes 1-4) such as isoprenaline, salbutamol, formoterol, salmeterol, terbutaline, orciprenaline, bitolterol mesylate, or pirbuterol, or a chiral enantiomer thereof.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a chromone, such as sodium cromoglycate or nedocromil sodium.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, with a glucocorticoid, such as flunisolide, triamcinolone acetonide, beclomethasone dipropionate, budesonide, fluticasone propionate, ciclesonide or mometasone furoate.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, with an agent that modulates a nuclear hormone receptor such as PPARs.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, together with an immunoglobulin

(Ig) or Ig preparation or an antagonist or antibody modulating Ig function such as anti-IgE (for example omalizumab).

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and another systemic or topically-applied anti-inflammatory agent, such as thalidomide or a derivative thereof, a retinoid, dithranol or calcipotriol.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and combinations of aminosalicylates and sulfapyridine such as sulfasalazine, mesalazine, balsalazide, and olsalazine; and immunomodulatory agents such as the thiopurines, and corticosteroids such as budesonide.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, together with an antibacterial agent such as a penicillin derivative, a tetracycline, a macrolide, a beta-lactam, a fluoroquinolone, metronidazole, an inhaled aminoglycoside; an antiviral agent including acyclovir, famciclovir, valaciclovir, ganciclovir, cidofovir, amantadine, rimantadine, ribavirin, zanamavir and oseltamavir; a protease inhibitor such as indinavir, nelfinavir, ritonavir, and saquinavir; a nucleoside reverse transcriptase inhibitor such as didanosine, lamivudine, stavudine, zalcitabine or zidovudine; or a non-nucleoside reverse transcriptase inhibitor such as nevirapine or efavirenz.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a cardiovascular agent such as a calcium channel blocker, a beta-adrenoceptor blocker, an angiotensin-converting enzyme (ACE) inhibitor, an angiotensin-2 receptor antagonist; a lipid lowering agent such as a statin or a fibrate; a modulator of blood cell morphology such as pentoxyfylline; thrombolytic, or an anticoagulant such as a platelet aggregation inhibitor.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and a CNS agent such as an antidepressant (such as sertraline), an anti-Parkinsonian drug (such as deprenyl, L-dopa, ropinirole, pramipexole, a MAOB inhibitor such as selegine and rasagiline, a comP inhibitor such as tasmar, an A-2 inhibitor, a dopamine reuptake inhibitor, an NMDA antagonist, a nicotine agonist, a dopamine agonist or an inhibitor of neuronal nitric oxide

synthase), or an anti-Alzheimer's drug such as donepezil, rivastigmine, tacrine, a COX-2 inhibitor, propentofylline or metrifonate.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, and an agent for the treatment of acute or chronic pain, such as a centrally or peripherally-acting analgesic (for example an opioid or derivative thereof), carbamazepine, phenytoin, sodium valproate, amitryptiline or other anti-depressant agent-s, paracetamol, or a non-steroidal anti-inflammatory agent.

The present invention further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, together with a parenterally or topically-applied (including inhaled) local anaesthetic agent such as lignocaine or a derivative thereof.

A compound of the present invention, or a pharmaceutically acceptable salt thereof, can also be used in combination with an anti-osteoporosis agent including a hormonal agent such as raloxifene, or a biphosphonate such as alendronate.

The present invention still further relates to the combination of a compound of the invention, or a pharmaceutically acceptable salt thereof, together with a: (i) tryptase inhibitor; (ii) platelet activating factor (PAF) antagonist; (iii) interleukin converting enzyme (ICE) inhibitor; (iv) IMPDH inhibitor; (v) adhesion molecule inhibitors including VLA-4 antagonist; (vi) cathepsin; (vii) kinase inhibitor such as an inhibitor of tyrosine kinase (such as Btk, Itk, Jak3 or MAP, for example Gefitinib or Imatinib mesylate), a serine / threonine kinase (such as an inhibitor of a MAP kinase such as p38, JNK, protein kinase A, B or C, or IKK), or a kinase involved in cell cycle regulation (such as a cylin dependent kinase); (viii) glucose-6 phosphate dehydrogenase inhibitor; (ix) kinin-B1. - or B2. -receptor antagonist; (x) anti-gout agent, for example colchicine; (xi) xanthine oxidase inhibitor, for example allopurinol; (xii) uricosuric agent, for example probenecid, sulfinpyrazone or benzbromarone; (xiii) growth hormone secretagogue; (xiv) transforming growth factor (TGFβ); (xv) platelet-derived growth factor (PDGF); (xvi) fibroblast growth factor for example basic fibroblast growth factor (bFGF); (xvii) granulocyte macrophage colony stimulating factor (GM-CSF); (xviii) capsaicin cream; (xix) tachykinin NK1 or NK3 receptor antagonist such as NKP-608C, SB-233412 (talnetant) or D-4418; (xx) elastase inhibitor such as UT-77 or ZD-0892; (xxi) TNF-alpha converting enzyme inhibitor (TACE); (xxii) induced nitric oxide synthase (iNOS) inhibitor; (xxiii) chemoattractant

receptor-homologous molecule expressed on TH2 cells, (such as a CRTH2 antagonist); (xxiv) inhibitor of P38; (xxv) agent modulating the function of Toll-like receptors (TLR), (xxvi) agent modulating the activity of purinergic receptors such as P2X7; or (xxvii) inhibitor of transcription factor activation such as NFkB, API, or STATS.

A compound of the invention, or a pharmaceutically acceptable salt thereof, can also be used in combination with an existing therapeutic agent for the treatment of cancer, for example suitable agents include:

(i) an antiproliferative/antineoplastic drug or a combination thereof, as used in medical oncology, such as an alkylating agent (for example cis-platin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan or a nitrosourea); an antimetabolite (for example an antifolate such as a fluoropyrimidine like 5-fluorouracil or tegafur, raltitrexed, methotrexate, cytosine arabinoside, hydroxyurea, gemcitabine or paclitaxel); an antitumour antibiotic (for example an anthracycline such as adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin or mithramycin); an antimitotic agent (for example a vinca alkaloid such as vincristine, vinblastine, vindesine or vinorelbine, or a taxoid such as taxol or taxotere); or a topoisomerase inhibitor (for example an epipodophyllotoxin such as etoposide, teniposide, amsacrine, topotecan or a camptothecin);

(ii) a cytostatic agent such as an antioestrogen (for example tamoxifen, toremifene, raloxifene, droloxifene or iodoxyfene), an oestrogen receptor down regulator (for example fulvestrant), an antiandrogen (for example bicalutamide, flutamide, nilutamide or cyproterone acetate), a LHRH antagonist or LHRH agonist (for example goserelin, leuprorelin or buserelin), a progestogen (for example megestrol acetate), an aromatase inhibitor (for example as anastrozole, letrozole, vorazole or exemestane) or an inhibitor of 5α-reductase such as finasteride;

(iii) an agent which inhibits cancer cell invasion (for example a metalloproteinase inhibitor like marimastat or an inhibitor of urokinase plasminogen activator receptor function);

(iv) an inhibitor of growth factor function, for example: a growth factor antibody (for example the anti-erbb2 antibody trastuzumab, or the anti-erbb1 antibody cetuximab [C225]), a farnesyl transferase inhibitor, a tyrosine kinase inhibitor or a serine/threonine kinase inhibitor, an inhibitor of the epidermal growth factor family (for example an EGFR family tyrosine kinase inhibitor such as N-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-

morpholinopropoxy)quinazolin-4-amine (gefitinib, AZD1839), N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) or 6-acrylamido-N-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)quinazolin-4-amine (CI 1033)), an inhibitor of the platelet-derived growth factor family, or an inhibitor of the hepatocyte growth factor family;

(v) an antiangiogenic agent such as one which inhibits the effects of vascular endothelial growth factor (for example the anti-vascular endothelial cell growth factor antibody bevacizumab, a compound disclosed in WO 97/22596, WO 97/30035, WO 97/32856 or WO 98/13354), or a compound that works by another mechanism (for example linomide, an inhibitor of integrin $\alpha v\beta 3$ function or an angiostatin);

(vi) a vascular damaging agent such as combretastatin A4, or a compound disclosed in WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 or WO 02/08213;

(vii) an agent used in antisense therapy, for example one directed to one of the targets listed above, such as ISIS 2503, an anti-ras antisense;

(viii) an agent used in a gene therapy approach, for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase patient tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; or

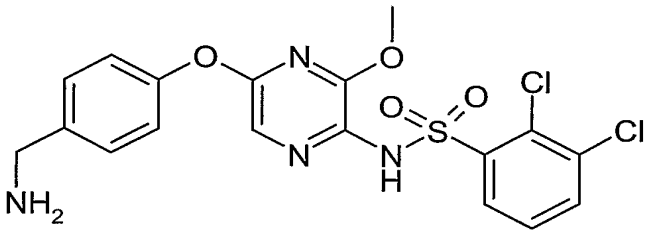
(ix) an agent used in an immunotherapeutic approach, for example ex-vivo and in-vivo approaches to increase the immunogenicity of patient tumour cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell anergy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumour cell lines and approaches using anti-idiotypic antibodies.

The present invention will now be further explained by reference to the following illustrative examples. In the examples the NMR spectra were measured on a Varian Unity spectrometer at a proton frequency of either 300 or 400 MHz. The MS spectra were measured on either an Agilent 1100 MSD G1946D spectrometer or a Hewlett Packard HP1100 MSD G1946A spectrometer. Preparative HPLC separations were performed using

a Waters Symmetry® or Xterra® column using 0.1% aqueous trifluoroacetic acid: acetonitrile, 0.1% aqueous ammonia: acetonitrile or 0.1% ammonium acetate: acetonitrile as the eluant.

Example 1

***N*-{5-[4-(Aminomethyl)phenoxy]-3-methoxypyrazinyl}-2,3-dichlorobenzenesulphonamide Trifluoroacetate salt**



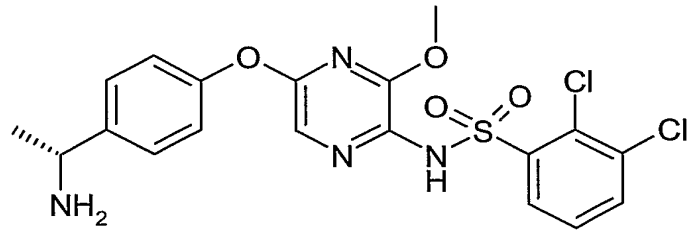
N-(5-bromo-3-methoxypyrazinyl)-2,3-dichloro-*N*-{[2-(trimethylsilyl)ethoxy]methyl}benzenesulphonamide (Example 55a, WO2003059893), (0.275g) and *tert*-butyl (4-hydroxybenzyl)carbamate (0.125g) were dissolved in 1-methyl-2-pyrrolidinone (4ml), treated with caesium carbonate (0.5g) and stirred at room temperature overnight. The reaction mixture was poured into 2N HCl (20ml) and extracted with ethyl acetate (3 x 20ml). The organic extract was evaporated to dryness to give a gum (0.28g). The gum was dissolved in dichloromethane (10ml) and treated with trifluoroacetic acid (2ml) and stirred for 2 hr. Toluene (25ml) was added and the reaction mixture was evaporated to dryness. The residue was triturated with ethyl acetate to afford a solid. Yield 0.05g.

m/e 455/457/459 ($M+1^+$, 100%).

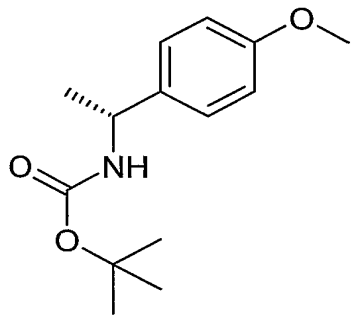
^{1}H NMR (D6-DMSO) δ 8.14 (1H, dd), 7.73 (1H, dd), 7.65 (3H, s) 7.48 (2H, d), 7.41 (1H, t), 7.34 (1H, s), 7.10 (2H, d), 4.03 (2H, s), 3.81 (3H, s).

Example 2

***N*-(5-{4-[(*R*)-1-Aminoethyl]phenoxy}-3-methoxypyrazinyl)-2,3-dichlorobenzenesulphonamide Hydrochloride salt**

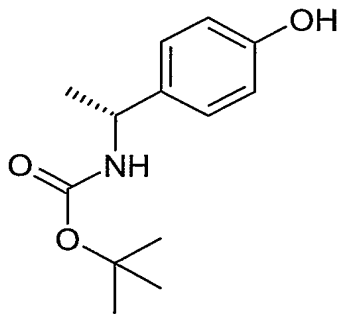


a) [(1*R*)-1-(4-Methoxyphenyl)ethyl]carbamic acid, 1,1-dimethylethyl ester



A solution of di-*tert*-butyl dicarbonate (15.9g) in dichloromethane (50ml) was added dropwise to a stirred solution of (1*R*)-1-(4-methoxyphenyl)ethanamine (10.0g) and triethylamine (10.1ml) in dichloromethane (120ml) at 0°C . The cooling bath was removed and the mixture was stirred overnight. The mixture was then washed with dilute aqueous hydrochloric acid and brine, dried ($MgSO_4$) and evaporated to dryness to give the product. Yield 18.5g. Used directly without further purification.

b) [(1*R*)-1-(4-Hydroxyphenyl)ethyl]carbamic acid, 1,1-dimethylethyl ester



Boron tribromide (170ml of a 1M solution in dichloromethane) was added over 3 h to a stirred solution of the product of step a (18.5g) in dry dichloromethane (155ml) cooled to 0°C. During the addition period, the cooling bath was allowed to expire so that the reaction mixture could attain room temperature. The reaction mixture was cooled back to 0°C and quenched by the careful addition of methanol (100ml) until the fizzing ceased. The solution was evaporated to dryness and methanol (100ml) was added and the solution evaporated (repeated 3 times). The residue was dissolved in dichloromethane (150ml) and triethylamine (20ml) and cooled to 0°C. Di-*tert*-butyl dicarbonate (16g) was added, the cooling bath was removed, and the mixture was stirred at room temperature overnight. The mixture was washed with dilute aqueous hydrochloric acid and brine, then dried ($MgSO_4$) and evaporated to dryness. The crude product was purified by silica gel chromatography eluting with *iso*-hexanes:ethyl acetate (75:25). Yield 11.0g.

m/e 237 (M^+), 166 (100%).

^{1}H NMR (CDCl3)): 7.13 (2H, br d), 6.74 (2H, d), 5.70 (1H, br s), 4.74 (2H, br d), 1.38-1.45 (12H, m).

c) *N*-(5-{4-[(*R*)-1-Aminoethyl]phenoxy}-3-methoxypyrazinyl)-2,3-dichlorobenzenesulphonamide Hydrochloride salt

N-(5-bromo-3-methoxypyrazinyl)-2,3-dichloro-*N*-{[2-(trimethylsilyl)ethoxy]methyl}benzenesulphonamide (Example 55a, WO2003059893), (0.275g) and the product from step b (0.13g) were dissolved in *N,N*-dimethylformamide (4ml), treated with caesium carbonate (0.5g) and stirred at room temperature overnight.

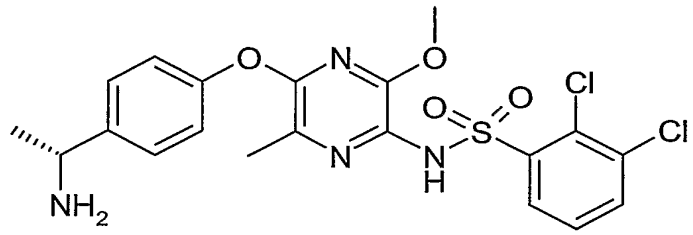
The reaction mixture was poured into 2N HCl (20ml) and extracted with ethyl acetate (3 x 20ml). The organic extract was evaporated to dryness to give a gum (0.22g). The gum was dissolved in dichloromethane (10ml) and treated with trifluoroacetic acid (2ml) and stirred for 2 hr. The reaction mixture was evaporated to dryness and passed down a silica gel column eluted with dichloromethane:methanol (95:5) to afford a solid which was dissolved in diethyl ether (10ml) and treated with 4N HCl in 1,4-dioxane (1ml), evaporated to dryness and then triturated with acetonitrile to afford a solid. Yield 0.025g.

m/e 469/471/473 ($M+1^+$).

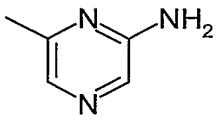
^{1}H NMR (D6-DMSO) δ 11.27(1H, br s), 8.48 (3H, br s), 8.04 (1H, d), 7.94 (1H, d), 7.59 (1H, t), 7.53 (2H, d), 7.48 (1H, s), 7.24 (2H, d), 4.41 (1H, q), 3.72 (3H, s), 1.52 (3H, d).

Example 3

***N*-(5-{4-[(*R*)-1-Aminoethyl]phenoxy}-3-methoxy-6-methylpyrazinyl)-2,3-dichlorobenzenesulphonamide Hydrochloride salt**



a) 6-Methyl-2-pyrazinamine



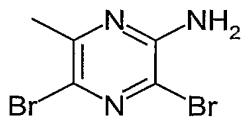
To a suspension of sodium hydride [60% dispersion in mineral oil] (11.2g,) in THF (60ml) at 0°C was added, diethylmalonate (2.1moleq) in THF (60ml) and 2,6-dichloropyrazine (20g) in THF (40ml). The mixture was then heated to reflux for 18hrs before being allowed to cool and 2M Hydrochloric acid (100ml) added. The resulting two layers were separated and the THF layer partially concentrated under vacuum to give a

solution containing 2-(6-chloro-pyrazin-2-yl)-malonic acid diethyl ester. This solution was then cooled to 10°C and 2M sodium hydroxide (328ml) added. After stirring for 24hrs the mixture was washed with methyl isobutyl ketone [MIBK] (200ml) and the organic layer discarded. The aqueous layer containing 2-(6-chloro-pyrazin-2-yl)-malonic acid was then added to 6M hydrochloric acid (135ml), maintaining a reaction temperature of 20-25°C to facilitate decarboxylation.

The resulting 6-chloro-pyrazin-2-yl-acetic acid partially precipitated from the mixture, but for ease of isolation was extracted into MIBK (130ml), dried using $MgSO_4$, filtered and evaporated to give a yellow solid. The resulting crude solid 22.4g was then crystallised from methyl-t-butyl ether (MTBE) to give pure 6-chloro-pyrazin-2-yl-acetic acid, 15.4g.

The 6-chloro-pyrazin-2-yl-acetic acid (20.0g) was then treated with aqueous ammonia (120ml) in a sealed vessel at 180°C (35 bar) for 8hrs. The mixture was then cooled to 20°C and water (40ml) added, before being concentrated under vacuum to remove the ammonia. The product was extracted into ethyl acetate and the solution treated with charcoal, before being dried using $MgSO_4$, filtered and evaporated to give 6-methyl-2-pyrazin-2-ylamine as a pale green solid 9.0g. Used directly without further purification.

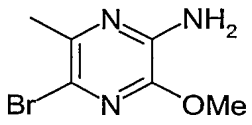
b) 3,5-Dibromo-6-methyl-2-pyrazinamine



6-Methyl-2-pyrazinamine (18g) was suspended/partially dissolved in acetonitrile (25 rel vol) and 2,6-lutidine (3 mol eq) was added. The solution was then cooled to 5°C and bromine (2.6 mol eq) was added. The mixture was then allowed to warm to room temperature (approximately 20°C), and stirred overnight. The mixture was quenched by the addition of sodium sulfite solution (10% w/v) and adjusted to a pH >8 by the addition of 40% w/w sodium hydroxide solution. The mixture was then distilled under reduced pressure 35°C to 40°C (125 mBar) to remove acetonitrile and 2,6-lutidine, before being

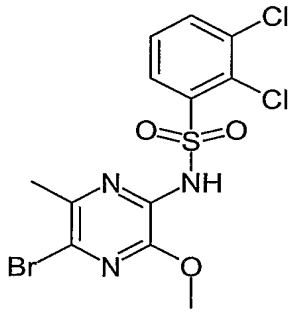
cooled to 10°C and stirred for one hour. The product was collected by filtration, washed with water and dried in a vacuum oven at 40°C, to give a brown solid 47g. Used directly

c) 5-Bromo-3-methoxy-6-methyl-2-pyrazinamine



3,5-Dibromo -6-methyl-2-pyrazinamine (45g) was suspended in methanol (5 rel vol) and 30% w/w sodium methoxide in methanol (1.5 mol eq) added. The mixture was then heated to 70°C. After 18 h less than 0.5% starting material was visible by GC/MS. Water (6.5 rel vol) was then added to the hot reaction mixture such that the reaction temperature did not drop below 50°C. Once the addition was complete the mixture was allowed to cool to room temperature (approximately 20°C) before being cooled to 5°C and stirred for two h. The product was then collected by filtration, washed and dried in a vacuum oven at 45°C. Yield 30.0g. Used directly

d) 2,3-Dichloro-*N*-[5-bromo-3-methoxy-6-methylpyrazinyl)benzenesulphonamide



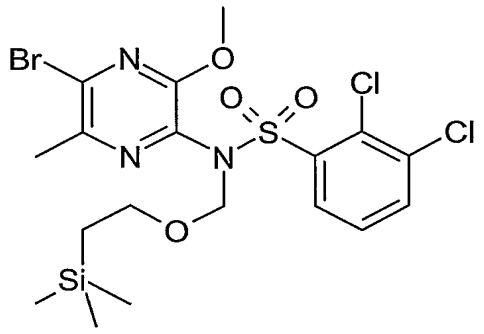
A solution of 5-bromo-3-methoxy-6-methyl-2-pyrazinamine (120g) and 2,3-dichlorobenzenesulphonylchloride (148.5g, 1.1 mol eq) in THF (500ml), was cooled to 0°C under a nitrogen atmosphere. A solution of potassium *tert*-butoxide in THF (1M, 1.21 litres, 2.2 mol eq) was then added to the reaction vessel, such that the temperature of the reaction mixture did not exceed 10°C. The time taken for the addition was approximately one hour. The reaction mixture was then stirred for one hour at 0°C, before being diluted

with water. The resulting mixture was then extracted with methyl *tert*-butyl ether [TBME] (2 litres) and ethyl acetate (2 x 1 litre). The combined organic extracts were then washed with 1M hydrochloric acid and the organic layer concentrated under reduced pressure. The resulting residue was triturated with TBME (500ml) and the mixture stirred for 16 h before the product was isolated via filtration. The resulting pale brown solid was dried in a vacuum oven at 45°C to constant weight. Yield 215.2g.

m/e 424/426/428 ($M-1^-$, 100%)

^{1}H NMR (DMSO) δ 8.16 (1H, dd), 7.95 (1H, dd), 7.62 (1H, t), 3.88 (3H, s), 2.16 (3H, s)

e) *N*-(5-Bromo-3-methoxy-6-methylpyrazinyl)-2,3-dichloro-*N*-{[2-(trimethylsilyl)ethoxy]methyl}benzenesulphonamide



N-Ethyl-*N*-isopropylpropan-2-amine (3.5 ml) was added to a stirred solution of *N*-(5-bromo-3-methoxy-6-methylpyrazinyl)-2,3-dichlorobenzenesulphonamide (4.25g) and [2-(chloromethoxy)ethyl](trimethyl)silane (2.5ml) in dichloromethane (75 ml), under an atmosphere of nitrogen gas, cooled in an ice-bath. *N*-(5-Bromo-3-methoxy-6-methylpyrazinyl)-2,3-dichlorobenzenesulphonamide may be prepared as in steps 3a) to 3d) above or alternatively by the method of Example 118 of WO2003059893. The ice-bath was removed and the mixture was stirred at room temperature overnight. The mixture was washed with water (2 x 50ml), 2N HCl (2 x 50ml), saturated aqueous sodium bicarbonate (50ml), brine (50ml), dried ($MgSO_4$) and evaporated down to an oil. This was triturated with *iso*-hexane to afford a solid. Yield 4.45g.

^{1}H NMR ($CDCl_3$) δ 8.02 (1H, dd), 7.69 (1H, dd), 7.32 (1H, t), 5.24 (2H, s), 3.89 (3H, s), 3.74 (2H, m), 2.47 (3H, s), 0.83 (2H, m), 0.01 (9H, s).

f) *N*-(5-{4-[(*R*)-1-Aminoethyl]phenoxy}-3-methoxy-6-methylpyrazinyl)-2,3-dichlorobenzenesulphonamide

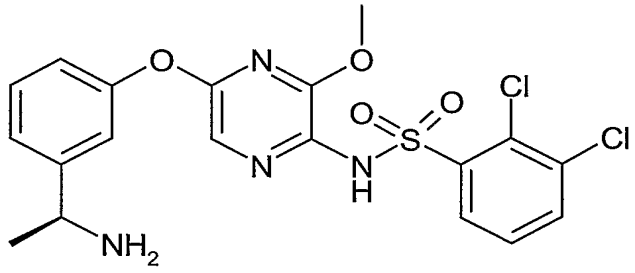
The product from step e (0.56g) and *tert*-butyl [(*R*)-1-(4-hydroxyphenyl)ethyl]carbamate (0.26g) were reacted as described in Example 2 to afford the title product as a solid. Yield 0.11g.

m/e 483/485/487 ($M+1^+$).

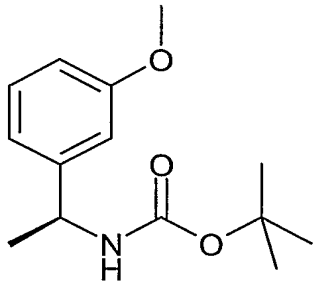
^{1}H NMR (D6-DMSO) δ 8.26 (3H, br s), 8.1 (1H, d), 7.74 (1H, d), 7.49 (1H, d), 7.45 (2H, d), 7.0 (2H, d), 4.4 (1H, q), 3.61 (3H, s), 1.96 (3H, s), 1.49 (3H, d).

Example 4

***N*-{5-[3-((S)-1-Aminoethyl)phenoxy]-3-methoxypyrazinyl}-2,3-dichlorobenzenesulphonamide Hydrochloride salt**

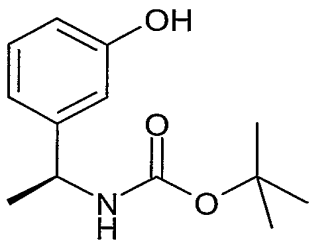


a) [(S)-1-(3-Methoxyphenyl)ethyl]carbamic acid, 1,1-dimethylethyl ester



Di-*tert*-butyl dicarbonate (3.0g) was added to a stirred solution of (S)-1-(3-methoxyphenyl)ethylamine (2.0g) and triethylamine (7.4ml) in dichloromethane (66ml). After 16h, the mixture was washed with aqueous saturated sodium bicarbonate solution, dried ($MgSO_4$) and evaporated to dryness to give the product. Yield 3.0g. Used directly without further purification.

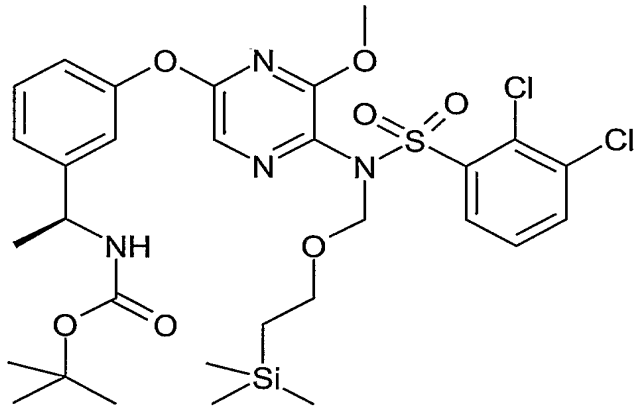
b) [(S)-1-(3-Hydroxyphenyl)ethyl]carbamic acid, 1,1-dimethylethyl ester



Boron tribromide (26ml of a 1M solution in dichloromethane) was added over 5 minutes to a stirred solution of the product of step a (3.0g) in dry dichloromethane (25ml) cooled to –78°C. After 0.5h the cooling bath was removed. After a further 0.5h at room temperature the reaction mixture was quenched by careful addition of methanol (100ml) until the fizzing stops. The solution was evaporated to dryness and methanol (100ml) added and the solution evaporated (repeated 2 times). The residue was dissolved in dichloromethane (60ml) and triethylamine (6.5ml). Di-*tert*-butyl dicarbonate (2.8g) was added and the mixture stirred at room temperature for 0.5h. The mixture was washed with aqueous saturated sodium bicarbonate solution, dried ($MgSO_4$) and evaporated to dryness to give the product. Yield 3.0g.

^{1}H NMR (CDCl3)): 7.17 (1H, t), 6.82 (1H, d), 6.76 (1H, br s), 6.7 (1H, dd), 4.7-4.9 (2H, br m), 1.56 (3H, d), 1.43 (9H, s).

c) [(1S)-1-[3-[[5-[[2,3-Dichlorobenzenesulphonyl]-[[2-[trimethylsilanyl]ethoxy]methyl]amino]-6-methoxypyrazinyl]oxy]phenyl]ethyl]carbamic acid, 1,1-dimethylethyl ester



The product from step b) (0.47g) was added to a stirred mixture of N-(5-bromo-3-methoxypyrazinyl)-2,3-dichloro-N-{[2-(trimethylsilanyl)ethoxy]methyl}benzenesulphonamide (Example 55a, WO2003059893) (0.72g) and caesium carbonate (2g) in dry 1-methyl-2-pyrrolidinone (7ml). After 16h, the mixture was diluted with water (100ml) and extracted with ethyl acetate (5 x 50ml). The combined organic solutions were dried (MgSO4) and evaporated. Purification was by silica gel chromatography eluting with *iso*-hexanes:ethyl acetate (80:20). Yield 0.9g.

^{1}H NMR ($CDCl_3$) δ 7.97 (1H, dd), 7.66 (1H, s), 7.64 (1H, dd), 7.35 (1H, t), 7.27 (1H, d), 7.25 (1H, d), 7.18 (1H, d), 7.1 (1H, s), 7.02 (1H, dd), 5.3 (1H, s), 5.23 (2H, s), 4.7-4.9 (3H, br s), 3.7-3.9 (2H, m), 3.66 (3H, s), 1.40 (9H, s), 0.8-0.95 (2H, m), 0.05 (9H, s).

d) *N*-{5-[3-((S)-1-Aminoethyl)phenoxy]-3-methoxypyrazinyl}-2,3-dichlorobenzenesulphonamide Hydrochloride salt

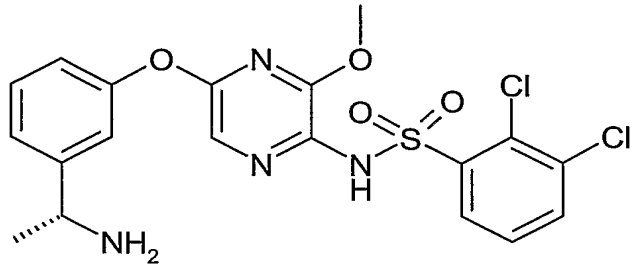
The product from step c) (0.9g) was dissolved in 4N HCl in 1,4-dioxane (2ml). After 2h, the mixture was evaporated to dryness. The solid was triturated with diethyl ether and collected. Yield 0.5g.

m/e 469/471/473 ($M+1^+$).

^{1}H NMR (D6-DMSO) δ 11.30 (1H, br s), 8.45 (3H, br s), 8.03 (1H, dd), 7.94 (1H, dd), 7.58 (1H, t), 7.52 (1H, s), 7.45 (1H, t), 7.3-7.35 (2H, m), 7.17 (1H, d), 4.38-4.5 (1H, m), 3.73 (3H, s), 1.48 (3H, d).

Example 5

***N*-{5-[3-((R)-1-Aminoethyl)phenoxy]-3-methoxypyrazinyl}-2,3-dichlorobenzenesulphonamide Hydrochloride salt**



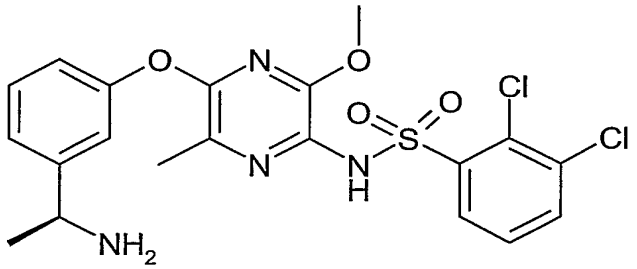
The title compound was prepared by the method of Example 4 using (R)-1-(3-methoxyphenyl)ethylamine (0.5g) in place of (S)-1-(3-methoxyphenyl)ethylamine. Yield 0.09g

m/e 469/471/473 ($M+1^+$).

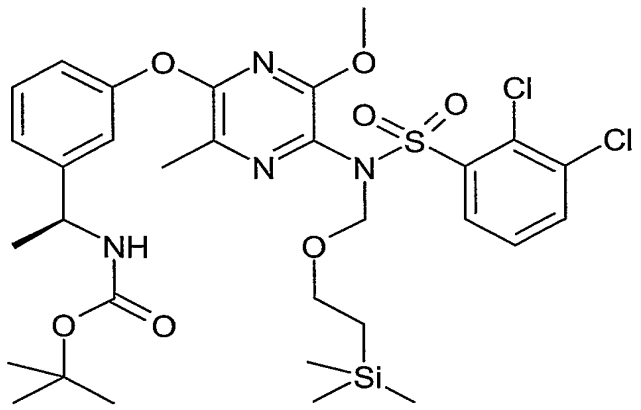
^{1}H NMR (D6-DMSO) δ 11.30 (1H, br s), 8.45 (3H, br s), 8.03 (1H, dd), 7.94 (1H, dd), 7.58 (1H, t), 7.52 (1H, s), 7.45 (1H, t), 7.3-7.35 (2H, m), 7.17 (1H, d), 4.38-4.5 (1H, m), 3.73 (3H, s), 1.48 (3H, d).

Example 6

***N*-{5-[3-((S)-1-Aminoethyl)phenoxy]-3-methoxy-6-methylpyrazinyl}-2,3-dichlorobenzenesulphonamide**



a) [(1S)-1-[3-[[5-[[(2,3-Dichlorobenzene)sulphonyl][[2-(trimethylsilanyl)ethoxy]methyl]amino]-6-methoxy-3-methylpyrazinyl]oxy]phenyl]ethyl]carbamic acid, 1,1-dimethylethyl ester



(S)-1-(3-Hydroxyphenyl)ethyl]carbamic acid *tert*-butyl ester (product of Example 4, step b) (0.9g) was added to stirred solution of *N*-(5-bromo-3-methoxy-6-methylpyrazinyl)-2,3-dichloro-*N*-{[2-(trimethylsilyl)ethoxy]methyl}benzenesulphonamide (product of Example 3, step e) (0.9g) and caesium carbonate (2g) in dry 1-methyl-2-pyrrolidinone (7ml). After 24h, the mixture was diluted with water (100ml) and extracted with ethyl acetate (5 x 50ml). The combined organic solutions were dried ($MgSO_4$) and evaporated. Purification was by silica gel chromatography eluting with *iso*-hexanes:ethyl acetate (75:25). Yield 0.8g. used directly

b) *N*-{5-[3-((S)-1-Aminoethyl)phenoxy]-3-methoxy-6-methylpyrazinyl}-2,3-dichlorobenzenesulphonamide

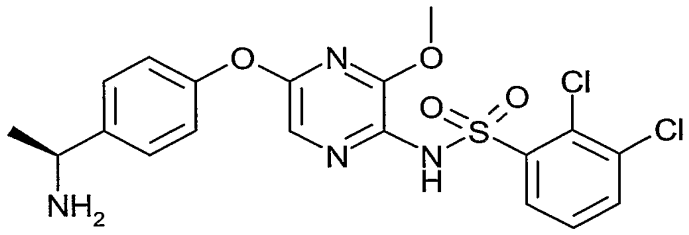
The product from step a (0.8g) was dissolved in 4N HCl in 1,4-dioxane (20ml). After 24h, the mixture was evaporated to dryness. Purification was by silica gel chromatography eluting with dichloromethane:methanol (9:1). Yield 0.2g.

m/e 483/485/487 ($M+1^+$).

^{1}H NMR (D6-DMSO) δ 8.3-8.5 (2H, br s), 8.10 (1H, dd), 7.91 (1H, d), 7.59 (1H, t), 7.42 (1H, t), 7.2-7.3 (2H, m), 7.08 (1H, d), 4.3-4.5 (1H, m), 3.62 (3H, s), 2.11 (3H, s), 1.46 (3H, d).

Example 7

***N*-(5-{4-[(*S*)-1-Aminoethyl]phenoxy}-3-methoxypyrazinyl)-2,3-dichlorobenzenesulphonamide.**



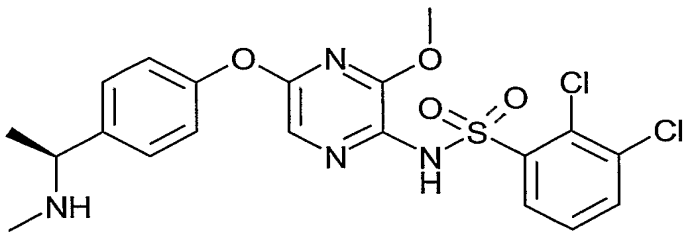
N-(5-bromo-3-methoxypyrazinyl)-2,3-dichloro-*N*-{[2-(trimethylsilyl)ethoxy]methyl}benzenesulphonamide (Example 55a, WO2003059893), (1.0 g) and *tert*-butyl [(*S*)-1-(4-hydroxyphenyl)ethyl]carbamate (0.45g) were dissolved in 1-methyl-2-pyrrolidinone (10ml), treated with caesium carbonate (0.6g) and stirred at room temperature overnight. The reaction mixture was poured into water (100 ml) and extracted with ethyl acetate (x2) ,dried ($MgSO_4$) evaporated under reduced pressure to give an oil (1.0 g). 0.4g of this oil was dissolved in dichloromethane (10ml) and 4 N HCl in 1,4-dioxane (5ml) added, stirred for 3 h and volatiles removed under reduced pressure. Purification was by silica gel chromatography eluting with dichloromethane:methanol, 9:1 to give the product as a solid. Yield 0.17g.

m/e 469/471/473 ($M+1^+$).

^{1}H NMR (D6-DMSO) δ 11.27(1H, br s), 8.48 (3H, br s), 8.04 (1H, d), 7.94 (1H, d), 7.59 (1H, t), 7.53 (2H, d), 7.48 (1H, s), 7.24 (2H, d), 4.41 (1H, q), 3.72 (3H, s), 1.52 (3H, d).

Example 8

2,3-Dichloro-*N*-(3-methoxy-5-{4-[(1S)-1-(methylamino)ethyl]phenoxy}pyrazinyl)benzenesulphonamide



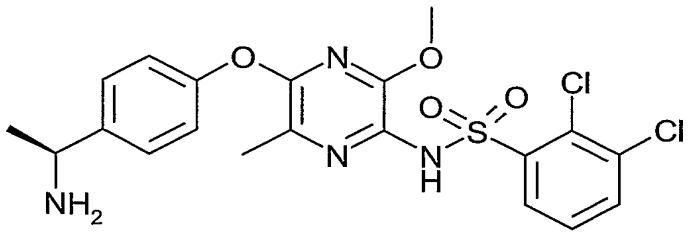
(5-bromo-3-methoxypyrazinyl)-2,3-dichloro-*N*-{[2-(trimethylsilyl)ethoxy]methyl}benzenesulphonamide (Example 55a, WO2003059893), (1.0 g) and *tert*-butyl [(*S*)-1-(4-hydroxyphenyl)ethyl]carbamate (0.45g) were dissolved in 1-methyl-2-pyrrolidinone (10ml), treated with caesium carbonate (0.6g) and stirred at room temperature overnight. The reaction mixture was poured into water (100ml) and extracted with ethyl acetate (x2), dried ($MgSO_4$) and evaporated under reduced pressure to give an oil (1.0 g). 0.4 g of this oil was dissolved in 1-methyl-2-pyrrolidinone (5ml), sodium hydride (0.09g of 60% dispersion in oil) added and the mixture stirred at room tremperature under nitrogen for 0.5h. Methyl iodide (0.25g) was added and the mixture stirred overnight. The reaction was poured into water, extracted with ethyl acetate (x2), dried ($MgSO_4$) and evaporated under reduced pressure. Purification was by silica gel chromatography eluting with *iso*-hexanes:ethyl acetate, 4:1 to give an oily gum (0.2g). This oily gum was dissolved in dichloromethane (5ml), 4 N HCl in 1,4-dioxane (10ml) was added, stirred for 3 h and volatiles were then removed under reduced pressure. Purification was by silica gel chromatography eluting with dichloromethane:methanol, 9:1 to give the product as a solid. Yield 0.04g.

m/e 483/485/487 ($M+1^+$).

^{1}H NMR (D6-DMSO) δ 11.29(1H, br s), 9.32 (1H, br s), 8.95 (1H, br s), 8.04-8.01 (1H, dd), 7.94-7.91 (1H, d), 7.58-7.49 (4H, m), 7.26-7.23 (2H, d), 4.31 (1H, br m), 3.73 (3H, s), 2.39 (3H, s), 1.55-1.54 (3H, d).

Example 9

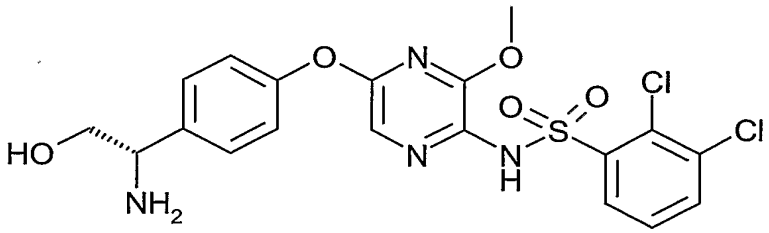
***N*-(5-{4-[(1*S*)-1-Aminoethyl]phenoxy}-3-methoxy-6-methylpyrazinyl)-2,3-dichlorobenzenesulphonamide Hydrochloride salt**



Prepared as example 3 using *tert*-butyl [(*S*)-1-(4-hydroxyphenyl)ethyl]carbamate (0.25g) in place of *tert*-butyl [(*R*)-1-(4-hydroxyphenyl)ethyl]carbamate. Yield 0.1g.
m/e 483/485/487 ($M+1^+$).
^{1}H NMR (D6-DMSO):11.21 (1H, s), 8.26 (3H, br s), 8.1 (1H, d), 7.74 (1H, d), 7.49 (1H, d), 7.45 (2H, d), 7.0 (2H, d), 4.4 (1H, q), 3.61 (3H, s), 1.96 (3H, s), 1.49 (3H, d).

Example 10

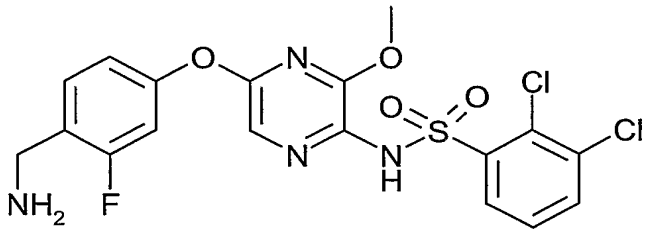
***N*-(5-{4-[(1*S*)-1-Amino-2-hydroxyethyl]phenoxy}-3-methoxypyrazinyl)-2,3-dichlorobenzenesulphonamide Trifluoroacetic acid salt**



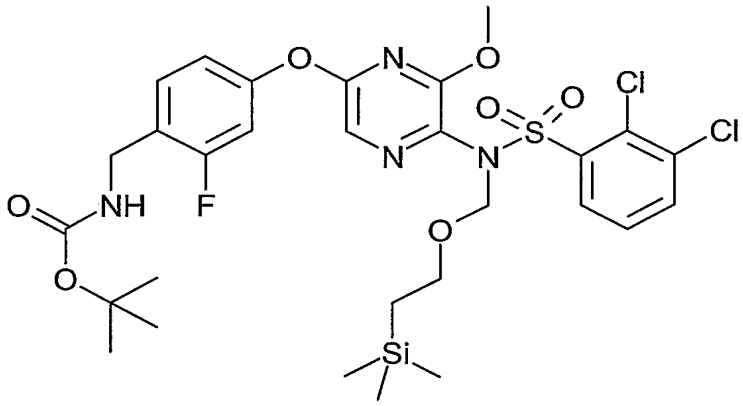
Prepared as example 1 using *tert*-butyl [(1*S*)-2-hydroxy-1-(4-hydroxyphenyl)ethyl]carbamate (0.13g) in place of *tert*-butyl (4-hydroxybenzyl)carbamate. Purification was by silica gel chromatography eluting with dichloromethane:methanol, 49:1 – 9:1, to give the product as a solid. Yield 0.18g.
m/e 485/487 ($M+1^+$).
^{1}H NMR (D6-DMSO):11.29 (1H, br s), 8.33 (3H, br s), 8.03 (1H, d), 7.94 (1H, d), 7.57 (1H, t), 7.46-7.52 (3H, m), 7.24 (2H, d), 5.56 (1H, br s), 4.31 (1H, br s), 3.62-3.76 (5H, m).

Example 11

***N*-{5-[4-(Aminomethyl)-3-fluorophenoxy]-3-methoxypyrazinyl}-2,3-dichlorobenzenesulphonamide, trifluoroacetic acid salt**



a) [[4-[[5-[[(2,3-Dichlorophenyl)sulphonyl][[2-(trimethylsilyl)ethoxy]methyl]amino]-6-methoxypyrazinyl]oxy]-2-fluorophenyl]methyl]carbamic acid, 1,1-dimethylethyl ester



Prepared by the method of Example 4 step c using *tert*-butyl (2-fluoro-4-hydroxybenzyl)carbamate (0.13g) in place of [(*S*)-1-(3-hydroxyphenyl)ethyl]carbamic acid, 1,1-dimethylethyl ester. Yield 0.25g. Used directly without further purification. m/e 687/689 ($M-15^-$), 471 (100%).

b) *N*-{5-[4-(Aminomethyl)-3-fluorophenoxy]-3-methoxypyrazinyl}-2,3-dichlorobenzenesulphonamide, trifluoroacetic acid salt

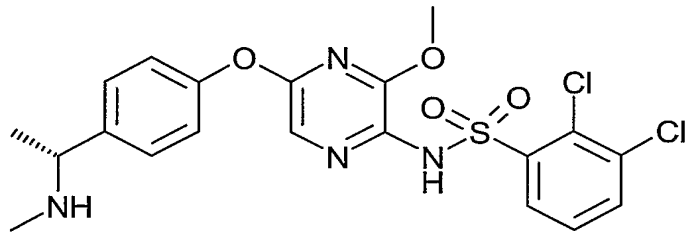
The product from step a (0.13g) was dissolved in dichloromethane (5ml) and treated with trifluoroacetic acid (2.5ml). The solution was stirred at room temperature for 1.75 h, then diluted with dichloromethane and concentrated onto silica gel *in-vacuo*. The resulting powder was purified by silica gel chromatography eluting with dichloromethane:methanol, 49:1 – 9:1, to give the product as a white foam. Yield 0.08g.

m/e 475/477 ($M+1^+$).

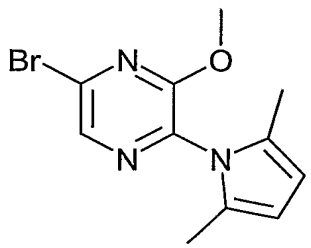
^{1}H NMR (D6-DMSO):11.35 (1H, br s), 8.19 (3H, br s), 8.04 (1H, d), 7.94 (1H, d), 7.50-7.60 (3H, m), 7.24 (1H, d), 7.09 (1H, d), 4.06 (2H, br s), 3.73 (3H, s).

Example 12

2,3-Dichloro-*N*-(3-methoxy-5-{4-[(1*R*)-1-(methylamino)ethyl]phenoxy}pyrazinyl)benzenesulphonamide Trifluoroacetic acid salt



a) 5-Bromo-2-(2,5-dimethyl-1*H*-pyrrol-1-yl)-3-methoxypyrazine

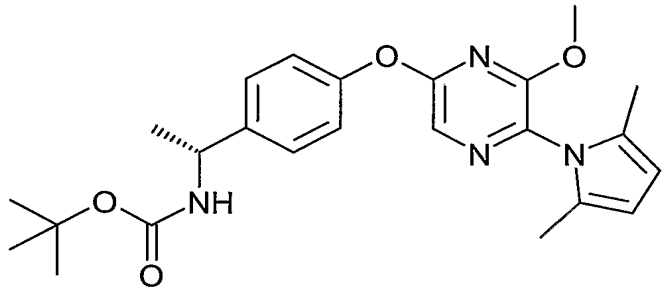


5-bromo-3-methoxy-2-pyrazinamine (13.5g), hexane-2,5-dione (9g) and para-toluenesulphonic acid hydrate (0.5g) in toluene (200ml) was heated under reflux using a Dean and Stark trap to collect the water. After 16h, the solution was allowed to cool,

concentrated to 50ml and passed through a pad of silica gel eluting with dichloromethane to collect the subtitle compound. Yield 17g.

^{1}H NMR (D6-DMSO):8.25 (1H, s), 5.92 (2H, s), 4.02 (3H, s), 2.02 (6H, s)

b) [(1*R*)-1-(4-{[5-(2,5-dimethyl-1*H*-pyrrol-1-yl)-6-methoxypyrazinyl]oxy}phenyl)ethyl]carbamic acid, 1,1-dimethylethyl ester

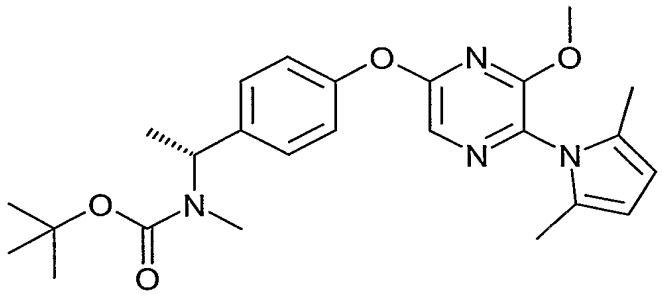


The product from step a (1.80g), *tert*-butyl [(*R*)-1-(4-hydroxyphenyl)ethyl]carbamate (Example 2 step b) (1.54g) and caesium carbonate (6.34g) in 1-methyl-2-pyrrolidinone (30ml) were stirred at room temperature overnight and at 40° for 3 h. The suspension was poured into dilute aqueous HCl and extracted into ethyl acetate. The combined organic phases were washed with water and brine, then dried ($MgSO_4$) and concentrated *in-vacuo* to give the subtitle compound as a brown foam. Yield 2.75g.

m/e 439 ($M+1^+$).

^{1}H NMR (D6-DMSO):7.92 (1H,s), 7.36-7.43 (4H, m), 7.29 (2H, d), 4.61-4.71 (1H, m), 3.74 (3H, s), 1.92 (6H, s), 1.31-1.41 (12H, m).

c) [(1*R*)-1-(4-{[5-(2,5-dimethyl-1*H*-pyrrol-1-yl)-6-methoxypyrazinyl]oxy}phenyl)ethyl]methylcarbamic acid, 1,1-dimethylethyl ester

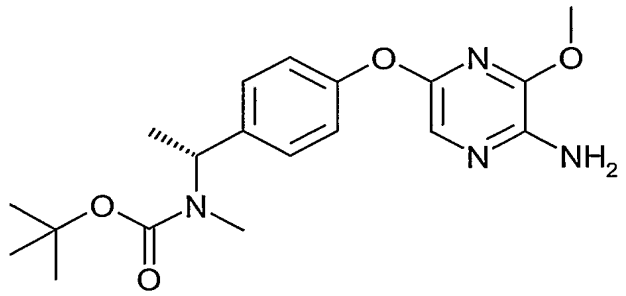


The product from step b (1.00g) in 1-methyl-2-pyrrolidinone (10ml) was treated with 60% sodium hydride suspension in mineral oil (0.18g) and stirred at room temperature for 30 minutes. Dimethylsulphate (0.43ml) was added, and the resulting mixture was stirred at room temperature for 4 h. The mixture was poured into dilute aqueous HCl and extracted into ethyl acetate. The combined organic phases were washed with water and brine, then dried ($MgSO_4$) and concentrated *in-vacuo* to give an orange gum. Purification was by silica gel chromatography eluting with isohexane:ethyl acetate, 85:15 to give the subtitle compound as a white foam. Yield 0.73g.

m/e 453 ($M+1^+$).

^1H NMR (D6-DMSO):7.95 (1H,s), 7.31-7.37 (6H, m), 3.73 (3H, s), 2.58 (3H, br s), 1.92 (6H, s), 1.48 (3H, br d), 1.41 (9H, br s).

d) ((1*R*)-1-{4-[(5-amino-6-methoxypyrazinyl)oxy]phenyl}ethyl)methylcarbamic acid, 1,1-dimethylethyl ester



A mixture of the product from step c (0.72g), hydroxylamine hydrochloride (1.25g), triethylamine (1.11ml), isopropanol (8ml) and water (2ml) was heated at reflux overnight. The solution was concentrated *in-vacuo* to remove the isopropanol, then diluted with water and extracted into ethyl acetate. The combined organic phases were washed with brine, then dried ($MgSO_4$) and concentrated onto silica gel *in-vacuo*. The resulting powder was purified by silica gel chromatography eluting with isohexane:ethyl acetate, 60:40 to give the subtitle compound as a white foam. Yield 0.51g.

m/e 375 ($M+1^+$).

^1H NMR (D6-DMSO):7.30 (1H, s), 7.21 (2H, d), 6.96 (2H, d), 6.14 (2H, br s), 5.28 (1H, br), 3.80 (3H, s), 2.53 (3H, s), 1.38-1.45 (12H, m).

e) 2,3-Dichloro-*N*-(3-methoxy-5-{4-[(1*R*)-1-(methylamino)ethyl]phenoxy}pyrazinyl)benzenesulphonamide Trifluoroacetic acid salt

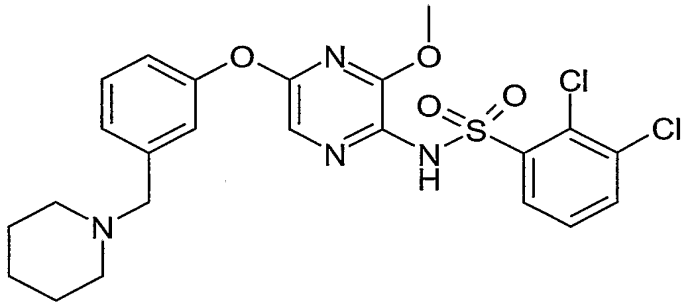
The product from step d (0.15g) and 2,3-dichlorobenzenesulphonyl chloride (0.10g) in THF (5ml) was cooled in ice-water and treated with 1 Molar potassium t-butoxide in THF (0.80ml). The dark brown solution was removed from the cooling bath and stirred at room temperature for 40 minutes. The reaction mixture was poured into dilute aqueous HCl and extracted into ethyl acetate. The combined organic phases were washed with brine, then dried ($MgSO_4$) and concentrated onto silica gel *in-vacuo*. The resulting powder was purified by silica gel chromatography eluting with isohexane:ethyl acetate, 75:25 to give an off-white foam (0.19g). The foam was dissolved in dichloromethane (5ml) and treated with trifluoroacetic acid (2.5ml). The solution was stirred at room temperature for 1 h, then diluted with dichloromethane and concentrated onto silica gel *in-vacuo*. The resulting powder was purified by silica gel chromatography eluting with dichloromethane:methanol, 49:1 – 19:1, to give the product as a solid. Yield 0.20g.

m/e 481/483/485 ($M-1^-$).

^{1}H NMR (D6-DMSO):11.29 (1H, br s), 9.00 (1H, br s), 8.78 (1H, br s), 8.03 (1H, d), 7.94 (1H, d), 7.57 (1H, t), 7.48-7.52 (3H, m), 7.26 (2H, d), 4.28-4.38 (1H, m), 3.73 (3H, s), 2.41-2.46 (3H, m), 1.53 (3H, d).

Example 13

2,3-Dichloro-*N*-{3-methoxy-5-[3-(1-piperidinylmethyl)phenoxy]pyrazinyl}benzenesulphonamide, Hydrochloride salt

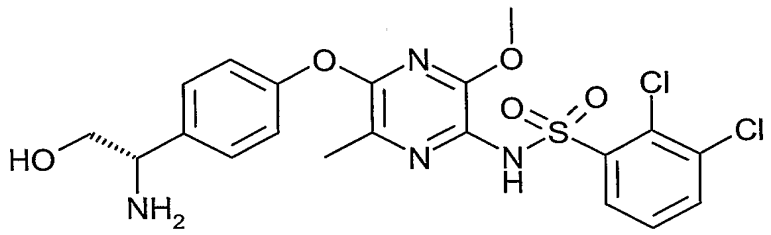


N-(5-bromo-3-methoxypyrazinyl)-2,3-dichloro-*N*-{[2-(trimethylsilyl)ethoxy]methyl}benzenesulphonamide (Example 55a, WO2003059893), (0.275g) and 3-(1-piperidinylmethyl)phenol (0.19g) were dissolved in *N,N*-dimethylformamide (4ml), treated with caesium carbonate (0.6g) and stirred at room temperature overnight. The reaction mixture was poured into 2N HCl (20ml) and extracted with ethyl acetate (3 x 20ml). The organic extract was evaporated to dryness to give a gum (0.2g). The gum was dissolved in dichloromethane (10ml) and treated with trifluoroacetic acid (2ml) and stirred for 2 hr. Toluene (25ml) was added and the reaction mixture was evaporated to dryness. The residue was triturated with 4N HCl in 1,4-dioxane (25ml), evaporated to dryness and then triturated with diethyl ether to afford a solid. Yield 0.11g. m/e 521/523/525 (M-1$^+$, 100%).

^{1}H NMR (D6-DMSO) δ 11.31 (1H, br s), 10.13 (1H, s), 8.05 (1H, d), 7.96 (1H, d) 7.76-7.4 (5H, m), 7.28 (1H, d), 4.25 (2H, s), 3.72 (3H, s) 3.34 (2H, m), 2.82 (2H, br s), 1.76 (4H, br s), 1.36 (2H, br s).

Example 14

***N*-[5-[4-[(1*S*)-1-Amino-2-hydroxyethyl]phenoxy]-3-methoxy-6-methylpyrazinyl]-2,3-dichlorobenzenesulphonamide Trifluoroacetic acid salt**



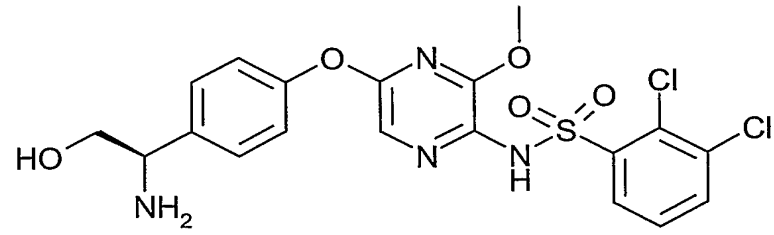
Prepared as Example 10 using the product from Example 3 step e (0.25g) in place of *N*-(5-bromo-3-methoxypyrazinyl)-2,3-dichloro-*N*-[[2-(trimethylsilyl)ethoxy]methyl]benzenesulfonamide. Yield 0.16g.

m/e 497/499 ($M-1^-$).

^{1}H NMR (D6-DMSO):11.24 (1H, br s), 8.31 (3H, br s), 8.12 (1H, d), 7.97 (1H, d), 7.62 (1H, t), 7.46 (2H, d), 7.17 (2H, d), 5.57 (1H, br s), 4.30 (1H, br s), 3.60-3.76 (5H, m), 2.14 (3H, s).

Example 15

***N*-[5-[4-[(1*R*)-1-Amino-2-hydroxyethyl]phenoxy]-3-methoxypyrazinyl]-2,3-dichlorobenzenesulphonamide Trifluoroacetic acid salt**



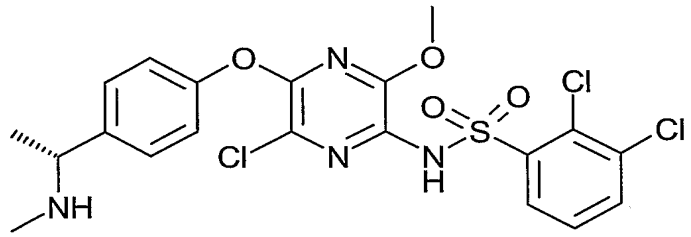
Prepared as Example 10 using (4*R*)-4-(4-hydroxyphenyl)-2,2-dimethyl-3-oxazolidinecarboxylic acid, 1,1-dimethylethyl ester (0.15g) in place of [(1*S*)-2-hydroxy-1-(4-hydroxyphenyl)ethyl]carbamic acid, 1,1-dimethylethyl ester. Yield 0.16g.

m/e 483/485 ($M-1^-$).

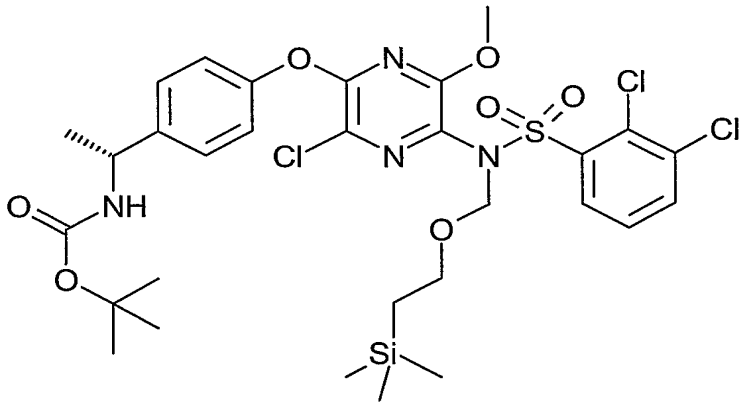
^{1}H NMR (D6-DMSO):11.43 (1H, br s), 8.46 (3H, br s), 8.18 (1H, d), 8.08 (1H, d), 7.71 (1H, t), 7.60-7.65 (3H, m), 7.38 (2H, d), 5.70 (1H, br s), 4.45 (1H, br s), 3.76-3.89 (5H, m).

Example 16

2,3-Dichloro-*N*-[6-chloro-3-methoxy-5-[4-[(1*R*)-1-(methylamino)ethyl]phenoxy]pyrazinyl]benzenesulfonamide Trifluoroacetic acid salt



a) [(1*R*)-1-[4-[[3-Chloro-5-[[(2,3-dichlorophenyl)sulphonyl][[2-(trimethylsilyl)ethoxy]methyl]amino]-6-methoxypyrazinyl]oxy]phenyl]ethyl]carbamic acid, 1,1-dimethylethyl ester



Prepared as Example 4 step c using *N*-(5-bromo-6-chloro-3-methoxypyrazinyl)-2,3-dichloro-*N*-[[2-(trimethylsilyl)ethoxy]methyl]benzenesulphonamide (Example 125, WO2003059893) (0.35g) in place of *N*-(5-bromo-3-methoxypyrazinyl)-2,3-dichloro-*N*-[[2-(trimethylsilyl)ethoxy]methyl]benzenesulphonamide and [(1*R*)-1-(4-

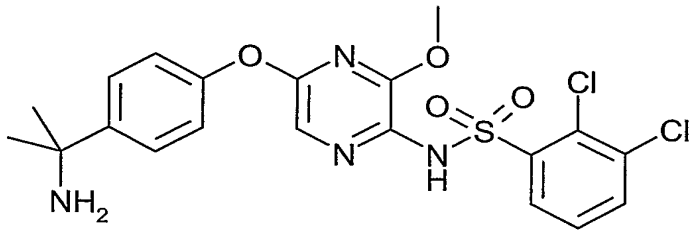
hydroxyphenyl)ethyl]carbamic acid, 1,1-dimethylethyl ester (Example 2 step b) (0.17g) in place of [(1*S*)-1-(3-hydroxyphenyl)ethyl]carbamic acid, 1,1-dimethylethyl ester. Yield 0.24g. Used directly without further purification.

b) 2,3-Dichloro-*N*-[6-chloro-3-methoxy-5-[4-[(1*R*)-1-(methylamino)ethyl]phenoxy]pyrazinyl]benzenesulphonamide Trifluoroacetic acid salt

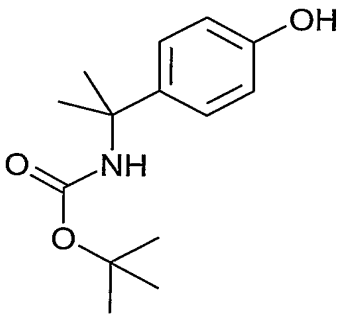
60% Sodium hydride suspension in mineral oil (0.041g) was added to an ice-cooled solution of the product from step a (0.24g) and dimethylsulphate (0.16ml) in 1-methyl-2-pyrrolidinone (5ml). After being stirred at 0°C for 30 minutes, the solution was poured into dilute hydrochloric acid and was extracted into ethyl acetate. The extracts were washed with brine, dried ($MgSO_4$) and concentrated onto silica gel *in-vacuo*. The resulting powder was purified by silica gel chromatography eluting with isohexane:ethyl acetate, 80:20 to give a white foam (0.17g). The foam was dissolved in dichloromethane (5ml) and treated with trifluoroacetic acid (5ml). The solution was stirred at room temperature for 45 minutes, then diluted with dichloromethane and concentrated onto silica gel *in-vacuo*. The resulting powder was purified by silica gel chromatography eluting with dichloromethane:methanol, 49:1 – 9:1, to give the product as a solid. Yield 0.21g.
m/e 517/519 ($M+1^+$).
^{1}H NMR (D6-DMSO):9.04 (1H, br s), 8.81 (1H, br s), 8.09 (1H, d), 7.91 (1H, d), 7.57 (1H, t), 7.48 (2H, d), 7.21 (2H, d), 4.27-4.37 (1H, m), 3.66 (3H, s), 2.42 (3H, t), 1.53 (3H, d).

Example 17

***N*-[5-[4-(1-Amino-1-methylethyl)phenoxy]-3-methoxypyrazinyl]-2,3-dichlorobenzenesulphonamide**



a) [1-(4-Hydroxyphenyl)-1-methylethyl]carbamic acid, 1,1-dimethylethyl ester

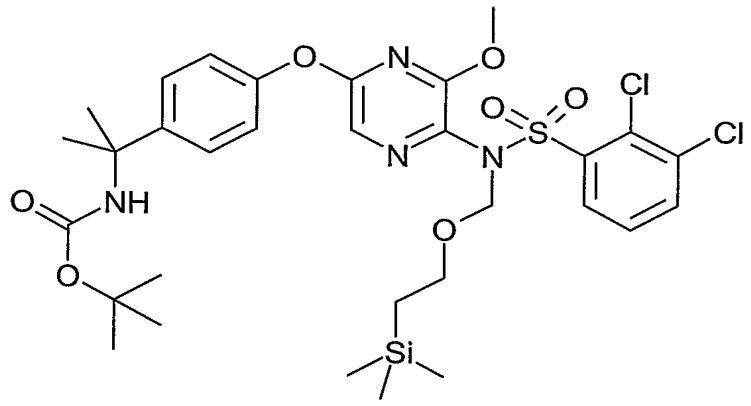


Prepared as Example 2 steps a and b using 4-methoxy-α,α-dimethyl-benzenemethanamine (0.73g) in place of (α*R*)-4-methoxy- α -methyl-benzenemethanamine. Purification was by silica gel chromatography eluting with isohexane:ethanol (90:10). Yield 0.39g.

m/e 251 (M^+), 180 (100%).

^{1}H NMR (CDCl3)): 7.20-7.28 (2H, m), 6.67-6.74 (2H, m), 1.20-1.65 (15H, m).

b) [1-[4-[[5-[[(2,3-Dichlorophenyl)sulphonyl][[2-(trimethylsilyl)ethoxy]methyl]amino]-6-methoxypyrazinyl]oxy]phenyl]-1-methylethyl]carbamic acid, 1,1-dimethylethyl ester



Prepared as Example 4 step c using the product from step a in place of [(1*S*)-1-(3-hydroxyphenyl)ethyl]carbamic acid, 1,1-dimethylethyl ester. Yield 0.24g. Used directly without further purification.

c) *N*-[5-[4-(1-Amino-1-methylethyl)phenoxy]-3-methoxypyrazinyl]-2,3-dichlorobenzenesulphonamide

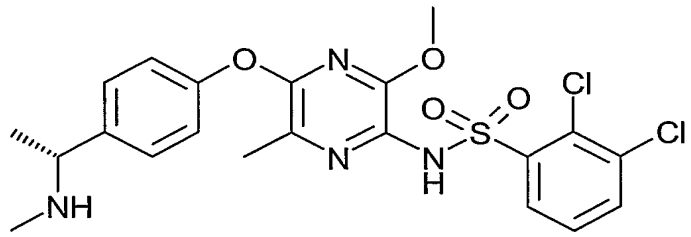
The product from step b (0.13g) was dissolved in a mixture of anhydrous diethyl ether (5ml) and 4M hydrogen chloride solution in 1,4-dioxane (5ml) and stirred at room temperature for 3 days, then diluted with diethyl ether and concentrated onto silica gel *in-vacuo*. The resulting powder was purified by silica gel chromatography eluting with dichloromethane:methanol, 49:1 – 9:1, to give a solid that was triturated with methanol, removed by filtration, and dried. Yield 0.03g.

m/e 481/483 ($M-1^-$).

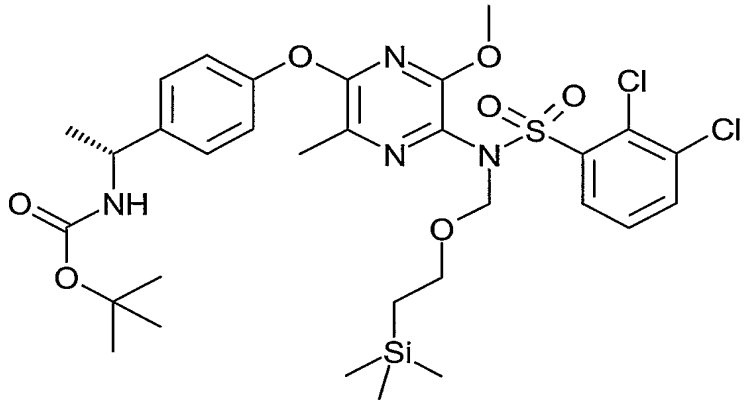
^{1}H NMR (D6-DMSO):8.22 (3H, br s), 7.96 (1H, d), 7.60 (1H, d), 7.46 (2H, d), 7.33 (1H, t), 7.07 (1H, s), 6.99 (2H, d), 3.67 (3H, s), 1.59 (6H, s).

Example 18

2,3-Dichloro-*N*-[3-methoxy-6-methyl-5-[4-[(1*R*)-1-(methylamino)ethyl]phenoxy]pyrazin-2-yl]-benzenesulphonamide, trifluoroacetic acid salt



a) [(1*R*)-1-[4-[[5-[[(2,3-Dichlorophenyl)sulphonyl][[2-(trimethylsilyl)ethoxy]methyl]amino]-6-methoxy-3-methylpyrazinyl]oxy]phenyl]ethyl]carbamic acid, 1,1-dimethylethyl ester



Prepared by the method of Example 4 step c using the product from Example 3 step e (0.25 g) in place of *N*-(5-bromo-3-methoxypyrazinyl)-2,3-dichloro-*N*-{[2-(trimethylsilanyl)ethoxy]methyl}benzenesulphonamide, and the product of Example 2 step b (0.16 g) in place of [(*S*)-1-(3-Hydroxyphenyl)ethyl]carbamic acid, 1,1-dimethylethyl ester. Yield 0.25 g.

m/e 697/699 ($M-15^-$), 464 (100%).

^{1}H NMR ($CDCl_3$) δ 7.98–8.04 (1H, m), 7.61-7.67 (1H, m), 7.23-7.34 (3H, m), 7.05-7.11 (2H, m), 5.21 (2H, s), 4.78 (2H, br s), 3.75-3.84 (2H, m), 3.53 (3H, s), 2.39 (3H, s), 1.35-1.51 (12H, m), 0.82-0.90 (2H, m), 0.01 (9H, s).

b) 2,3-Dichloro-*N*-[3-methoxy-6-methyl-5-[4-[(1*R*)-1-(methylamino)ethyl]phenoxy]pyrazin-2-yl]-benzenesulphonamide, trifluoroacetic acid salt

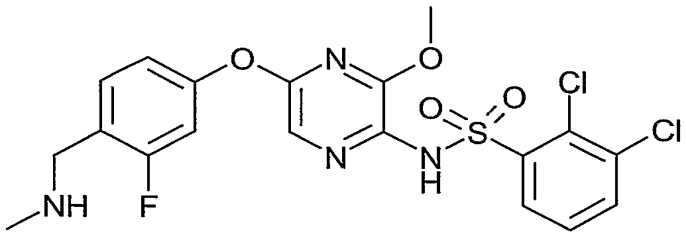
60% Sodium hydride suspension in mineral oil (21mg) was added to a solution of the product from step a (0.24g) in 1-methyl-2-pyrrolidinone (3ml), the mixture was stirred for 40 minutes at room temperature, then cooled in ice-water and treated with dimethylsulphate (64ul). After stirring at room temperature for 1 h more, sodium hydride (20mg) was added, the mixture was stirred at 50°C for 1 h, then more dimethylsulphate (64ul) was added and the mixture was stirred at 50°C overnight. More sodium hydride (75mg) and dimethylsulphate (128ul) were added and the mixture was stirred at 50°C for a further 1.5 h. The cooled mixture was then poured into dilute hydrochloric acid and extracted twice with ethyl acetate. The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated onto silica gel *in-vacuo*. The resulting powder was purified by silica gel chromatography eluting with isohexane:ethyl acetate, 85:15 to give a colourless residue (96mg). The residue was dissolved in dichloromethane (3ml) and treated with trifluoroacetic acid (1.5ml). The solution was stirred at room temperature for 30 minutes, then diluted with dichloromethane and concentrated onto silica gel *in-vacuo*. The resulting powder was purified by silica gel chromatography eluting with dichloromethane:methanol, 49:1 – 19:1, to give the product as a white foam. Yield 0.10g.

m/e 497/499 ($M+1^+$), 100%.

^{1}H NMR (D6-DMSO): 11.22 (1H, br s), 9.06 (1H, br s), 8.83 (1H, br s), 8.08-8.12 (1H, m), 7.92-7.96 (1H, m), 7.60 (1H, t), 7.45-7.50 (2H, m), 7.16-7.21 (2H, m), 4.32 (1H, br s), 3.61 (3H, s), 2.42 (3H, br s), 2.13 (3H, s), 1.53 (3H, d).

Example 19

2,3-Dichloro-*N*-(3-methoxy-5-{4-[(methylamino)methyl]phenoxy}pyrazin-2-yl)benzenesulfonamide, trifluoroacetic acid salt



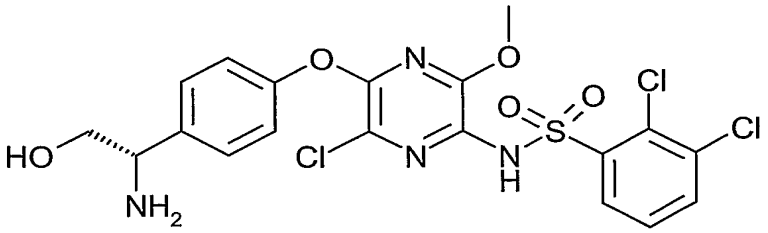
Dimethylsulphate (87ul) and 60% sodium hydride suspension in mineral oil (74mg) were added to an ice-cooled solution of the product from Example 11 step a (0.13g) in 1-methyl-2-pyrrolidinone (5ml) under an atmosphere of nitrogen. The cooling bath was removed and the mixture was stirred for 2.75 h at room temperature. The mixture was then poured into dilute hydrochloric acid and extracted twice with ethyl acetate. The combined extracts were washed with brine, dried ($MgSO_4$) and concentrated onto silica gel *in-vacuo*. The resulting powder was purified by silica gel chromatography eluting with isohexane:ethyl acetate, 85:15 to give a colourless residue (61mg). The residue was dissolved in dichloromethane (2ml) and treated with trifluoroacetic acid (1ml). The solution was stirred at room temperature for 1.5 h, then diluted with dichloromethane and concentrated onto silica gel *in-vacuo*. The resulting powder was purified by silica gel chromatography eluting with dichloromethane:methanol, 49:1 – 9:1, to give the product as a white foam. Yield 0.13g.

m/e 485/487 ($M-1^-$), 100%.

^1H NMR (D6-DMSO): 11.37 (1H, br s), 8.88 (2H, br s), 8.02-8.06 (1H, m), 7.89-7.94 (1H, br d), 7.52-7.59 (3H, m), 7.21-7.27 (1H, br d), 7.06-7.12 (1H, br d), 4.16 (2H, br s), 3.73 (3H, s), 2.59 (3H, br s).

Example 20

***N*-[5-[4-[(1*S*)-1-Amino-2-hydroxyethyl]phenoxy]-6-chloro-3-methoxypyrazinyl]-2,3-dichlorobenzenesulphonamide, trifluoroacetic acid salt**



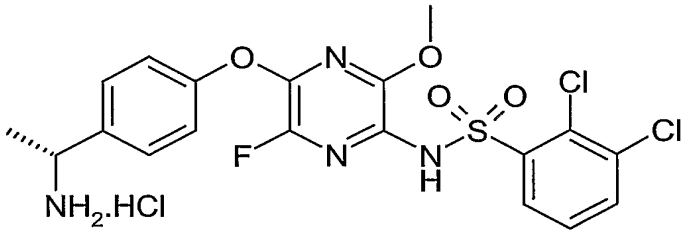
Prepared by the method of Example 10 using *N*-(5-bromo-6-chloro-3-methoxypyrazinyl)-2,3-dichloro-*N*-[[2-(trimethylsilyl)ethoxy]methyl]benzenesulphonamide (Example 125, WO2003059893) (0.49g) in place of *N*-(5-bromo-3-methoxypyrazinyl)-2,3-dichloro-*N*-[[2-(trimethylsilyl)ethoxy]methyl]benzenesulphonamide. Yield 0.12g.

m/e 519/521 ($M+1^+$), 504(100%).

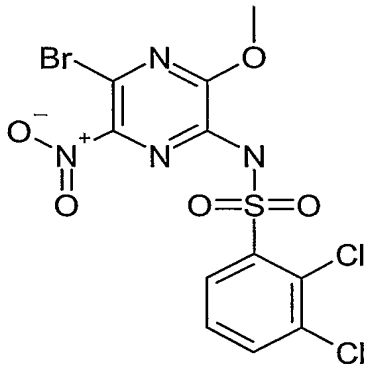
^{1}H NMR (D6-DMSO): 8.32 (3H, br s), 8.09-8.14 (1H, m), 7.92-7.98 (1H, m), 7.61 (1H, t), 7.44-7.51 (2H, m), 7.17-7.25 (2H, m), 5.57 (1H, br s), 4.26-4.37 (1H, br s), 3.62-3.77 (5H, m).

Example 21

***N*-(5-{4-[(1*R*)-1-Aminoethyl]phenoxy}-6-fluoro-3-methoxypyrazin-2-yl)-2,3-dichlorobenzenesulfonamide hydrochloride**



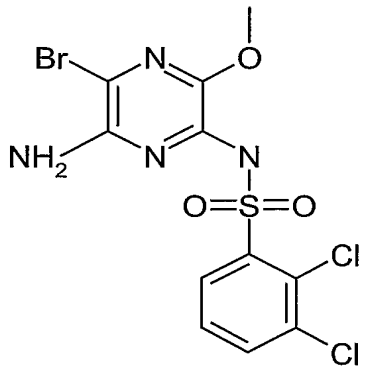
a) *N*-(5-Bromo-3-methoxy-6-nitropyrazinyl)-2,3-dichloro-benzenesulfonamide



Nitronium tetrafluoroborate (7.5g) was added portionwise over about 15 minutes to a stirred suspension of *N*-(5-bromo-3-methoxypyrazinyl)-2,3-dichloro-benzenesulfonamide (WO2003059893, example 8) (10.0g) in acetonitrile (100ml). After 2 h, further nitronium tetrafluoroborate (0.75g) was added. After a further 1 h, the reaction mixture was poured onto ice/water and extracted with dichloromethane. The extracts were dried ($MgSO_4$) and evaporated. Purification by silica gel chromatography, eluting with ethyl acetate:isohexane 1:1 afforded the subtitled product. Yield 8.4g.

1H NMR ($CDCl_3$): 8.36 (1H, m), 7.74 (1H, m), 7.49 (1H, t), 4.18 (3H, s).

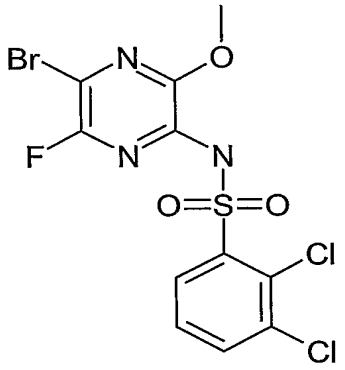
b) *N*-(6-Amino-5-bromo-3-methoxypyrazinyl)-2,3-dichloro-benzenesulfonamide



The product from step a (7.4g) in ethyl acetate (100ml) and acetic acid (50ml) containing 5% palladium on charcoal (Johnson Matthey type 39 paste) (3.2g) was put under hydrogen (1 bar) with vigorous stirring. After 3h, the reaction mixture was filtered through a pad of celite and evaporated. Yield 6.5g. Used directly without further purification.

m/e 427/429 ($M+1^+$)

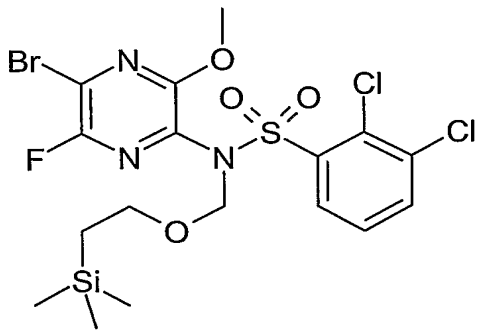
c) *N*-(5-Bromo-6-fluoro-3-methoxypyrazinyl)-2,3-dichloro-benzenesulfonamide



Sodium nitrite (2.4g) was added portionwise over about 20 minutes to a stirred solution of the product of step b (6.5g) in hydrogen fluoride-pyridine (pyridinium poly(hydrogen fluoride)) (30ml) cooled to –10°C. After 0.5 h, water was added and the solution extracted with dichloromethane (x2). The combined extracts were washed with water and then passed through a silica gel pad eluting with 1.25% methanol in dichloromethane. Purification by silica gel chromatography eluting with methanol:dichloromethane 1:100 afforded the subtitled product. Yield 4.1g.

m/e 430/432 ($M+1^+$)

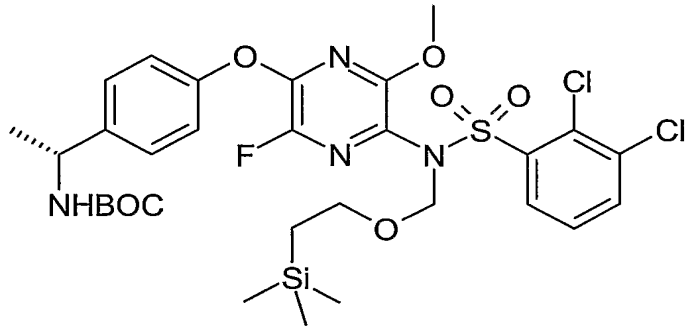
d) *N*-(5-Bromo-6-fluoro-3-methoxy-pyrazin-2-yl)-2,3-dichloro-N-(2-trimethylsilanyl-ethoxymethyl)-benzenesulfonamide



[2-(chloromethoxy)ethyl](trimethyl)silane (1.51ml) was added to a stirred solution of *N*-ethyl-*N*-isopropylpropan-2-amine (1.49 ml) and the product of step c (3.5g) in

dichloromethane (35 ml), under an atmosphere of nitrogen gas, at such a rate as to maintain the temperature below 5°C. After 30 minutes the reaction mixture was allowed to warm to room temperature then was washed with water and saturated brine. The organic phase was then dried ($MgSO_4$) and evaporated down to a light brown oil. Purification by silica gel chromatography eluting with isohexane:dichloromethane 1:3 gave the subtitle compound as a colourless oil, which was used without further purification. Yield 4.2 g.

e) *tert*-Butyl [(1*R*)-1-(4-{[5-([(2,3-dichlorophenyl)sulfonyl]{[2-(trimethylsilyl)ethoxy]methyl}amino)-3-fluoro-6-methoxypyrazin-2-yl]oxy}phenyl)ethyl]carbamate



Caesium carbonate (0.87 g) was added in one portion to a stirred solution of the product from step d (0.5 g) and [1-(4-hydroxy-phenyl)-ethyl]-carbamic acid *tert*-butyl ester (0.24 g) in dry 1-methyl-2-pyrrolidinone (15 ml). After 4 h, the mixture was poured onto water and extracted with ethyl acetate. A small amount of saturated brine solution was added to achieve separation. The organic phase was then washed with water and saturated brine solution then dried ($MgSO_4$) and evaporated. Purification by silica gel chromatography eluting with isohexane:ethyl acetate (3:1) gave the subtitle compound as a colourless oil. Yield 0.34 g.

m/e 616/618 ($M+H^+$)-BOC

f) *N*-(5-{4-[(1*R*)-1-Aminoethyl]phenoxy}-6-fluoro-3-methoxypyrazin-2-yl)-2,3-dichlorobenzenesulfonamide hydrochloride

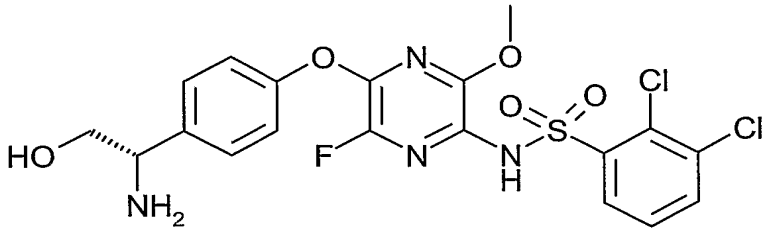
The product from step e was dissolved in 4N HCl in 1,4-dioxane (3 ml). After 16 h a further portion of 4N HCl in 1,4-dioxane (1 ml) was added and the solution was stirred at room temperature for 4 h. The mixture was then evaporated to dryness and the residue was purified by silica gel chromatography eluting with methanol:dichloromethane (5-10%) to give the title compound as a grey solid. Yield 0.13 g.

m/e 485 ($M-1^-$).

^{1}H NMR (D6-DMSO) δ 8.03-8.00 (1H, m), 7.67-7.64 (1H, m), 7.43-7.37 (3H, m), 6.96 (2H, d), 4.42-4.35 (1H, m), 3.68 (3H, s), 1.47 (3H, d).

Example 22

***N*-[5-[4-[(1*S*)-1-Amino-2-hydroxyethyl]phenoxy]-6-fluoro-3-methoxypyrazin-2-yl]-2,3-dichlorobenzenesulphonamide, trifluoroacetic acid salt**



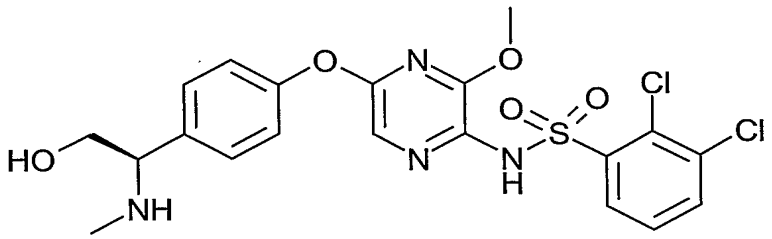
Prepared by the method of Example 10 using the product of example 21 step d (0.25g) in place of *N*-(5-bromo-3-methoxypyrazinyl)-2,3-dichloro-*N*-[[2-(trimethylsilyl)ethoxy]methyl]benzenesulphonamide. Yield 0.06g.

m/e 501/503 ($M-1^-$), (100%).

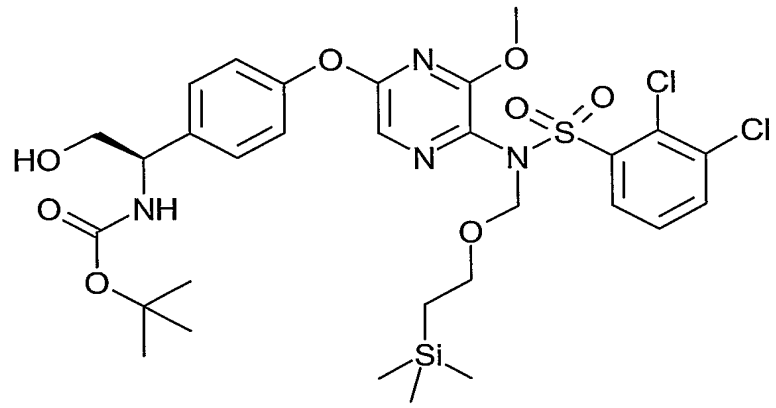
^{1}H NMR (D6-DMSO): 8.31 (3H, br s), 8.05-8.09 (1H, m), 7.89-7.94 (1H, m), 7.57 (1H, t), 7.43-7.48 (2H, m), 7.17-7.23 (2H, m), 5.55 (1H, br s), 4.25-4.33 (1H, m), 3.61-3.73 (5H, m).

Example 23

2,3-Dichloro-*N*-[5-[4-[(1*R*)-2-hydroxy-1-(methylamino)ethyl]phenoxy]-3-methoxypyrazin-2-yl]benzenesulphonamide, trifluoroacetic acid salt



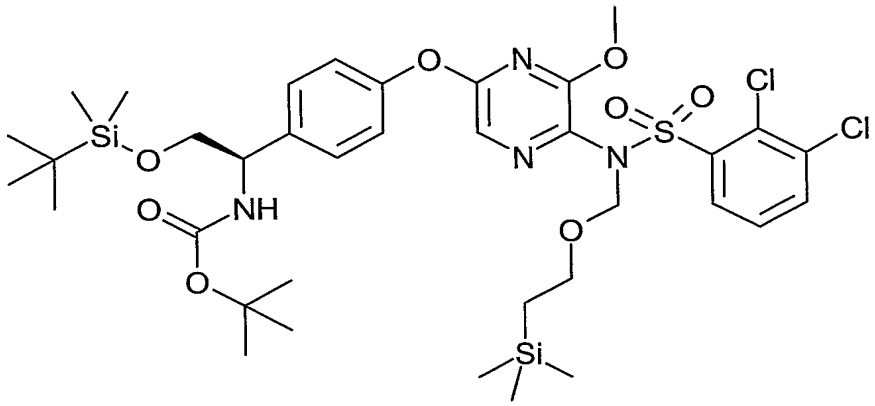
a) [(1*R*)-1-[4-[[5-[[(2,3-Dichlorophenyl)sulphonyl][[2-(trimethylsilyl)ethoxy]methyl]amino]-6-methoxypyrazinyl]oxy]phenyl]-2-hydroxyethyl]carbamic acid, 1,1-dimethylethyl ester



Prepared by the method of Example 4 step c using [(1*R*)-2-hydroxy-1-(4-hydroxyphenyl)ethyl]carbamic acid, 1,1-dimethylethyl ester (0.47g) in place of [(*S*)-1-(3-hydroxyphenyl)ethyl]carbamic acid, 1,1-dimethylethyl ester. Purification was by silica gel chromatography eluting with isohexanes:ethyl acetate (55:45). Yield 0.91g.

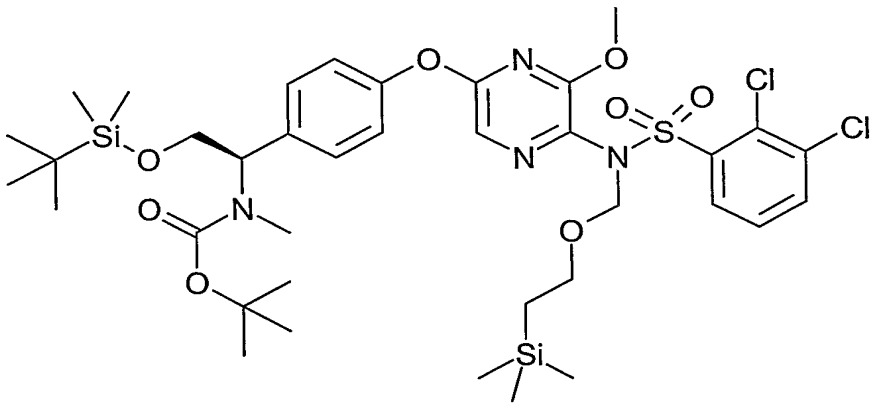
^{1}H NMR ($CDCl_3$) δ 7.95–8.00 (1H, m), 7.67 (1H, s), 7.62-7.66 (1H, m), 7.32-7.37 (2H, m), 7.27 (1H, t), 7.12-7.19 (2H, m), 5.23 (3H, s), 4.75-4.85 (1H, br m), 3.76-3.93 (4H, m), 3.67 (3H, s), 1.44 (9H, br s), 0.83-0.91 (2H, m), 0.01 (9H, s).

b) [(1*R*)-1-[4-[[5-[[(2,3-Dichlorophenyl)sulphonyl][[2-(trimethylsilyl)ethoxy]methyl]amino]-6-methoxypyrazinyl]oxy]phenyl]-2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]carbamic acid, 1,1-dimethylethyl ester



Imidazole (42mg) and *tert*-butyldimethylsilyl chloride (95mg) were added to a solution of the product from step a (0.41g) in N,N-dimethylformamide (5ml). The solution was stirred at room temperature for 2 h, then more imidazole (24mg) and *tert*-butyldimethylsilyl chloride (36mg) were added and the mixture was stirred overnight. The solution was poured into water and extracted twice with isohexane. The organic extracts were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford the subtitled compound as a white foam. Yield 0.45g. Used directly without further purification.
m/e 794/796 ($M-Cl^-$), 466(100%).

c) [(1*R*)-1-[4-[[5-[[(2,3-Dichlorophenyl)sulphonyl][[2-(trimethylsilyl)ethoxy]methyl]amino]-6-methoxypyrazinyl]oxy]phenyl]-2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]methylcarbamic acid, 1,1-dimethylethyl ester



Dimethyl sulphate (57ul) and 1 molar potassium *tert*-butoxide solution in THF (0.60ml) were added to a solution of the product from step b (0.45g) in THF (10ml) and the resulting mixture was stirred at room temperature for 1.25 h. More dimethyl sulphate (26ul) and 1 molar potassium *tert*-butoxide solution in THF (0.30ml) were added and the mixture was stirred for a further 2.75 h. The mixture was then poured into dilute hydrochloric acid and extracted twice with isohexane. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated onto silica gel *in-vacuo*. The resulting powder was purified by silica gel chromatography eluting with isohexane:acetone, 85:15 to give the subtitled compound as a white foam. Yield 0.37g. Used directly without further purification.

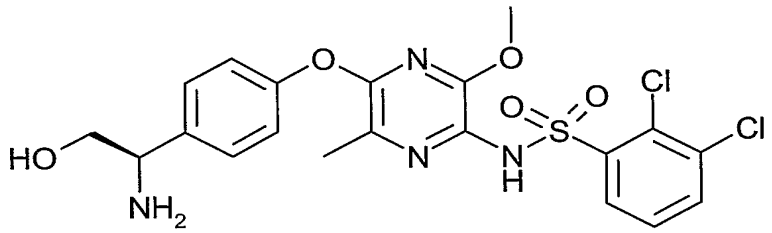
d) 2,3-Dichloro-*N*-[5-[4-[(1*R*)-2-hydroxy-1-(methylamino)ethyl]phenoxy]-3-methoxypyrazin-2-yl]benzenesulphonamide, trifluoroacetic acid salt

Prepared by the method of Example 11 step b using the product from step c (0.37g) in place of [[4-[[5-[[(2,3-dichlorophenyl)sulphonyl][[2-(trimethylsilyl)ethoxy]methyl]amino]-6-methoxypyrazinyl]oxy]-2-fluorophenyl]methyl]carbamic acid, 1,1-dimethylethyl ester. Yield 0.20g. m/e 499/501 ($M+1^+$), 468(100%).

^{1}H NMR (D6-DMSO):11.30 (1H, br s), 8.95 (2H, br s), 7.99-8.06 (1H, m), 7.90-7.97 (1H, m), 7.46-7.61 (4H, m), 7.21-7.30 (2H, m), 5.69 (1H, br s), 4.28 (1H, br s), 3.70-3.85 (5H, m), 2.42 (3H, br s).

Example 24

***N*-[5-[4-[(1*R*)-1-Amino-2-hydroxyethyl]phenoxy]-3-methoxy-6-methylpyrazin-2-yl]-2,3-dichlorobenzenesulphonamide, trifluoroacetic acid salt**



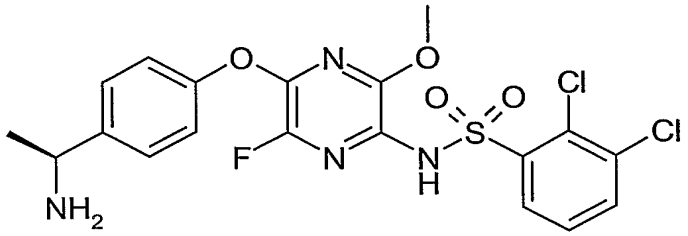
Prepared by the method of example 14 using [(1*R*)-2-hydroxy-1-(4-hydroxyphenyl)ethyl]carbamic acid, 1,1-dimethylethyl ester (0.13g) in place of *tert*-butyl [(1*S*)-2-hydroxy-1-(4-hydroxyphenyl)ethyl]carbamate. Yield 0.16g.

m/e 497/499/501 ($M-1^-$).

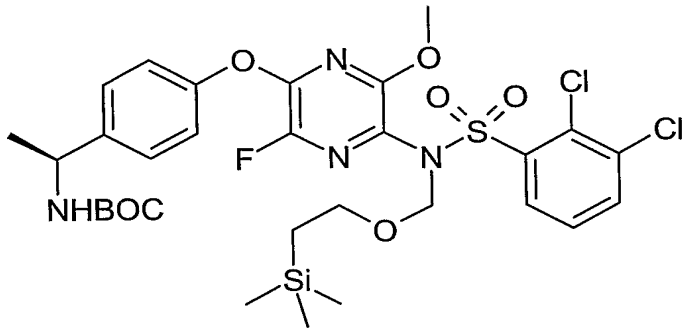
^{1}H NMR (D6-DMSO):11.22 (1H, br s), 8.31 (3H, br s), 8.07-8.13 (1H, m), 7.92-7.98 (1H, d), 7.60 (1H, t), 7.41-7.49 (2H, m), 7.12-7.19 (2H, m), 5.56 (1H, br s), 4.29 (1H, br s), 3.59-3.75 (5H, m), 2.13 (3H, s).

Example 25

***N*-(5-{4-[(1*S*)-1-aminoethyl]phenoxy}-6-fluoro-3-methoxypyrazin-2-yl)-2,3-dichlorobenzenesulfonamide**



a) [1-(4-{5-[(2,3-Dichloro-benzenesulfonyl)-(2-trimethylsilanyl-ethoxymethyl)-amino]-3-fluoro-6-methoxy-pyrazin-2-yloxy}-phenyl)-ethyl]-carbamic acid tert-butyl ester



Caesium carbonate (0.247 g) was added in one portion to a stirred solution of *N*-(5-Bromo-6-fluoro-3-methoxy-pyrazin-2-yl)-2,3-dichloro-N-(2-trimethylsilanyl-ethoxymethyl)-benzenesulfonamide (0.142 g) and [1-(4-hydroxy-phenyl)-ethyl]-carbamic acid *tert*-butyl ester (0.06 g) in dry 1-methyl-2-pyrrolidinone (5 ml). After 3 h, the mixture was poured onto water and extracted with ethyl acetate. The organic phase was then washed with water and saturated brine solution then dried ($MgSO_4$) and evaporated. Purification by silica gel chromatography eluting with isohexane:ethyl acetate (4:1) gave the subtitle compound as a colourless oil. Yield 0.13 g. BOC is *tert*-butoxycarbonyl.

m/e 615/617 $(M-1^-)$-BOC

b) *N*-(5-{4-[(1*S*)-1-aminoethyl]phenoxy}-6-fluoro-3-methoxypyrazin-2-yl)-2,3-dichlorobenzenesulfonamide

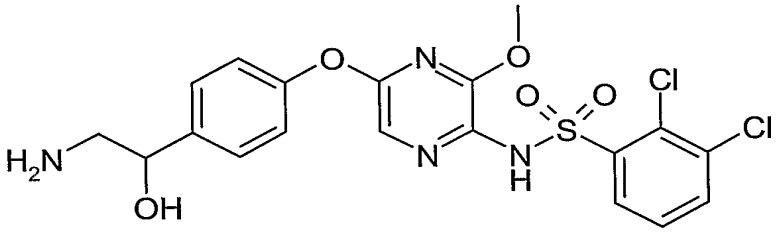
[1-(4-{5-[(2,3-Dichloro-benzenesulfonyl)-(2-trimethylsilanyl-ethoxymethyl)-amino]-3-fluoro-6-methoxy-pyrazin-2-yloxy}-phenyl)-ethyl]-carbamic acid *tert*-butyl ester (0.13 g) was dissolved in 4N HCl in 1,4-dioxane (2 ml). After 16 h, the mixture was evaporated to dryness. Methanol was added then evaporated under reduced pressure to remove any excess acid. The residue was purified by silica gel chromatography eluting with methanol:dichloromethane (5-10%) to give a solid which was further triturated with 10% methanol:dichloromethane to give the title compound as a colourless solid. Yield 22 mg.

m/e 485 ($M-1^-$).

^{1}H NMR (D6-DMSO): 8.04-8.00 (1H, m), 7.68-7.64 (1H, m), 7.43-7.37 (3H, m), 6.96 (2H, d), 4.42-4.34 (1H, m), 3.69 (3H, s), 1.47 (3H, d).

Example 26

***N*-{5-[4-(2-amino-1-hydroxyethyl)phenoxy]-3-methoxypyrazin-2-yl}-2,3-dichlorobenzenesulfonamide**



Prepared by the method of example 1 using 4-(2-amino-1-hydroxyethyl)phenol in place of *tert*-butyl (4-hydroxybenzyl)carbamate. Yield 0.09g.

m/e 485/487 ($M+H^+$).

^{1}H NMR (D6-DMSO): 11.25 (1H, s), 8.02 (1H, m), 7.90 (4H, m), 7.57 (1H, t), 7.43 (3H, m), 7.19 (2H, m), 6.09 (1H, s), 4.79 (1H, d), 3.73 (3H, s), 3.05 (1H, m), 2.86 (1H, m).

Pharmacological Data

FMAT Whole cell binding assay

Cells

CHO-K1 cells stably expressing the human recombinant CCR4 receptor (Euroscreen; Brussels, Belgium) were cultured in NUT.MIX.F_12(HAM) medium with glutamax-1, containing 10% (v/v) foetal bovine serum and 400 $\mu g\, ml^{-1}$ geneticin.

Cells were harvested at approximately 70% confluence by treatment with a cell dissociation buffer, and seeded at $5x10^3$ cells/100µl culture medium into wells of a black Costar clear-bottomed 96-well microtitre plates. Plates were incubated overnight at 37°C in 5% CO_2 and used the following day.

Assay

Before use, the cell plates were washed twice with 100 µl Hanks balanced salt solution (HBSS). To each well was then added 65µl of HBSS, 10 µL of 10% DMSO in HBSS ± test compound and then 25 µL of 2.8 nM FB-MDC (Applied Biosystems). This fluorescent probe was prepared from a 10 µM stock in 0.08% (v/v) TFA/16% (v/v) acetonitrile, diluted into HBSS.

After two hours incubation in the dark at room temperature, the plates were analysed in an FMAT8100 reader (Applied Biosystems) to measure fluorescence that was associated with binding of FB-MDC to the cells. Compound activity was determined as an pIC_{50} [-log(concentration of compound that results in 50% inhibition)], comparing fluorescence in control and background wells.

Measurement of Plasma Protein Binding

The extent of plasma protein binding was determined via equilibrium dialysis of a compound between human plasma and aqueous buffer at 37°C and determination of the concentration of compound in the plasma and buffer by HPLC-MS/MS.

Method

Dialysis cells (molecular weight cut-off 5000) were prepared by rinsing with water followed by soaking in the dialysis buffer for a minimum of 1 hour. The dialysis buffer was isotonic buffered saline pH 7.4. Stock solutions of compound in dimethylsulphoxide were prepared at a concentration of 1mM. Frozen pooled Human plasma was obtained from volunteers.

The stock DMSO solution of a compound was added to the plasma at a ration of 10 µl of DMSO to each ml of plasma. This gave a 1% DMSO in plasma solution with each compound at a concentration of 10 µM.

Dialysis cells were then prepared and one half of the cell filled with 700 µl of dialysis buffer and the other half of the cell with 700 µl of plasma solution of compound. Once prepared the cells were sealed and immersed in a water bath at 37°C. These cells were then rotated for a minimum of 4 hours to equilibrate.

After equilibration 500 µl of the buffer samples were removed and added to HPLC vials along with 100 µl of plasma (sample in 6-fold diluted plasma), and 100 µl of the plasma samples were removed and added to HPLC vials along with 500 µl of dialysis buffer (sample in 6-fold diluted plasma).

The samples were then analysed using HPLC-MS/MS. A four point calibration curve was obtained by dilutions of the stock solutions with 6-fold diluted plasma at concentrations of 0.05 μM, 0.15 μM, 0.5 μM and 2.5 μM which were injected in this order followed by the buffer sample and then the plasma sample.

Calculation

The concentration of compound in the samples were determined using MassLynx version 4.0 software (produced by Waters/Micromass) that automatically calculated a calibration curve and the concentration of compound in the cells. Plasma protein binding was determined from the calibration curve as the percentage of compound bound in human plasma (% bound) using the following equation wherein the factor in the numerator accounts for the small dilution of the aqueous samples with plasma and the factor of 6 in the denominator serves to correct for the 6-fold dilution of the plasma samples with buffer;

$$\%\text{bound} = 100 - 100\left(\frac{1.2\left(\frac{\text{Buffer concentration x Standard Injection vol.}}{\text{Buffer injection vol.}}\right)}{6\left(\frac{\text{Plasma concentration x Standard injection vol.}}{\text{Plasma injection vol.}}\right)}\right)$$

Results

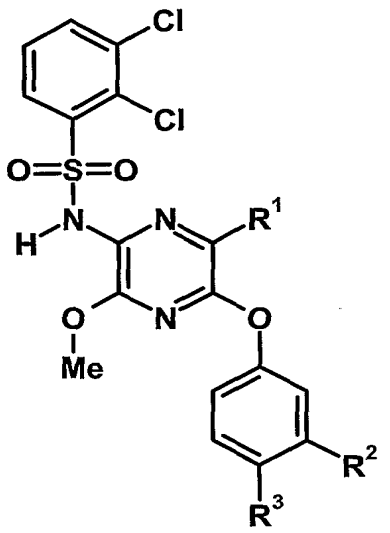
The compounds of the examples have a pIC50 of at least 6.0. Moreover, in the plasma protein binding assay the compounds of the examples have %bound to human plasma of less than 99.0%. This combination of high potency and low plasma protein binding to human plasma makes the compounds attractive for in vivo use

The following table shows the pIC_{50} and %bound figures for a representative selection of compounds according to the invention and a comparative compound from WO 03/059893 (Example 73, 4-[5-(2,3-Dichlorobenzenesulphonylamino)-6-methoxy-2-pyrazinyloxy]benzoic acid). The % bound figure of the comparative compound is 99.4 meaning that the amount unbound and thus available in vivo would be 0.6 %: the % bound figure for the compounds of the invention are significantly lower meaning the compounds will be more efficacious in vivo.

Compound of Example No.	FMAT CCR4 pIC_{50}	% Bound Human Plasma (% unbound)
6	8.1	96.4 (3.6)
11	7.7	97.8 (2.2)
12	7.6	95.8 (4.2)
14	7.0	95.6 (4.4)
Ex 73. WO/03059893	6.7	99.4 (0.6)

CLAIMS

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:

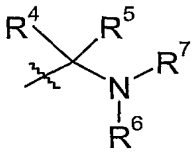


(I)

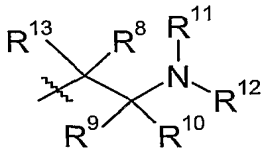
wherein

R^1 represents hydrogen, methyl, fluorine or chlorine;

one of R^2 and R^3 represents hydrogen or fluorine and the other of R^2 and R^3 represents a group of formula (IIA) or (IIB)



(IIA),



(IIB);

R^4 and R^5 each independently represent hydrogen, methyl or CH_2OH;

R^6 and R^7 each independently represent hydrogen, methyl, ethyl, or R^6 and R^7 together with the nitrogen atom to which they are attached form a 4-7 membered saturated heterocyclic ring;

R^8 represents hydrogen or methyl;

R^{13} represents hydrogen, methyl or hydroxyl;

R^9 and R^{10} each independently represent hydrogen or methyl; and

R^{11} and R^{12} each independently represent hydrogen, methyl, ethyl, or R^{11} and R^{12} together with the nitrogen atom to which they are attached form a 4-7 membered saturated heterocyclic ring.

2. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein one of R^2 and R^3 represents hydrogen or fluorine and the other of R^2 and R^3 represents a group of formula (IIA).

3. A compound according to claim 1 or claim 2, or a pharmaceutically acceptable salt thereof, wherein R^1 represents hydrogen or methyl.

4. A compound according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein R^4 and R^5 each independently represent hydrogen or methyl.

5. A compound according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein R^4 and R^5 each independently represent hydrogen or CH_2OH.

6. A compound according to any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein R^6 and R^7 each independently represent hydrogen or methyl.

7. A compound according to any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein R^3 represents a group of formula (IIA) and R^2 represents hydrogen.

8. A compound according to any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein R^2 represents a group of formula (IIA) and R^3 represents hydrogen.

9. A compound according to claim 1 which is

N-{5-[4-(Aminomethyl)phenoxy]-3-methoxypyrazinyl}-2,3-dichlorobenzenesulphonamide,

N-(5-{4-[(*R*)-1-Aminoethyl]phenoxy}-3-methoxypyrazinyl)-2,3-dichlorobenzenesulphonamide,

N-(5-{4-[(*R*)-1-Aminoethyl]phenoxy}-3-methoxy-6-methylpyrazinyl)-2,3-dichlorobenzenesulphonamide,

N-{5-[3-((S)-1-Aminoethyl)phenoxy]-3-methoxypyrazinyl}-2,3-dichlorobenzenesulphonamide,

N-{5-[3-((R)-1-Aminoethyl)phenoxy]-3-methoxypyrazinyl}-2,3-dichlorobenzenesulphonamide,

N-{5-[3-((S)-1-Aminoethyl)phenoxy]-3-methoxy-6-methylpyrazinyl}-2,3-dichlorobenzenesulphonamide,

N-(5-{4-[(*S*)-1-Aminoethyl]phenoxy}-3-methoxypyrazinyl)-2,3-dichlorobenzenesulphonamide,

2,3-Dichloro-*N*-(3-methoxy-5-{4-[(1S)-1-(methylamino)ethyl]phenoxy}pyrazinyl)benzenesulphonamide,

N-(5-{4-[(1*S*)-1-Aminoethyl]phenoxy}-3-methoxy-6-methylpyrazinyl)-2,3-dichlorobenzenesulphonamide,

N-(5-{4-[(1*S*)-1-Amino-2-hydroxyethyl]phenoxy}-3-methoxypyrazinyl)-2,3-dichlorobenzenesulphonamide,

N-{5-[4-(Aminomethyl)-3-fluorophenoxy]-3-methoxypyrazinyl}-2,3-dichlorobenzenesulphonamide,

2,3-Dichloro-*N*-(3-methoxy-5-{4-[(1*R*)-1-(methylamino)ethyl]phenoxy}pyrazinyl)benzenesulphonamide,

2,3-Dichloro-*N*-{3-methoxy-5-[3-(1-piperidinylmethyl)phenoxy]pyrazinyl}benzenesulphonamide,

N-[5-[4-[(1*S*)-1-Amino-2-hydroxyethyl]phenoxy]-3-methoxy-6-methylpyrazinyl]-2,3-dichlorobenzenesulphonamide,

N-[5-[4-[(1*R*)-1-Amino-2-hydroxyethyl]phenoxy]-3-methoxypyrazinyl]-2,3-dichlorobenzenesulphonamide,

2,3-Dichloro-*N*-[6-chloro-3-methoxy-5-[4-[(1*R*)-1-(methylamino)ethyl]phenoxy]pyrazinyl]benzenesulfonamide,

N-[5-[4-(1-Amino-1-methylethyl)phenoxy]-3-methoxypyrazinyl]-2,3-dichlorobenzenesulphonamide,

2,3-Dichloro-*N*-[3-methoxy-6-methyl-5-[4-[(1*R*)-1-(methylamino)ethyl]phenoxy]pyrazin-2-yl]-benzenesulphonamide,

2,3-Dichloro-*N*-(3-methoxy-5-{4-[(methylamino)methyl]phenoxy}pyrazin-2-yl)benzenesulfonamide,

N-[5-[4-[(1*S*)-1-Amino-2-hydroxyethyl]phenoxy]-6-chloro-3-methoxypyrazinyl]-2,3-dichlorobenzenesulphonamide,

N-(5-{4-[(1*R*)-1-Aminoethyl]phenoxy}-6-fluoro-3-methoxypyrazin-2-yl)-2,3-dichlorobenzenesulfonamide,

N-[5-[4-[(1*S*)-1-Amino-2-hydroxyethyl]phenoxy]-6-fluoro-3-methoxypyrazin-2-yl]-2,3-dichlorobenzenesulphonamide,

2,3-Dichloro-*N*-[5-[4-[(1*R*)-2-hydroxy-1-(methylamino)ethyl]phenoxy]-3-methoxypyrazin-2-yl]benzenesulphonamide,

N-[5-[4-[(1*R*)-1-Amino-2-hydroxyethyl]phenoxy]-3-methoxy-6-methylpyrazin-2-yl]-2,3-dichlorobenzenesulphonamide,

N-(5-{4-[(1*S*)-1-aminoethyl]phenoxy}-6-fluoro-3-methoxypyrazin-2-yl)-2,3-dichlorobenzenesulfonamide

N-{5-[4-(2-amino-1-hydroxyethyl)phenoxy]-3-methoxypyrazin-2-yl}-2,3-dichlorobenzenesulfonamide

or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 9 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

11. A compound of formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 9 for use in therapy.

12. Use of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 9 in the manufacture of a medicament for use in the treatment of asthma.

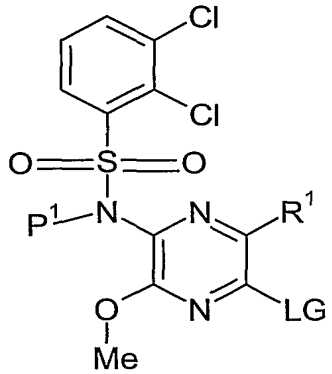
13. A method of treating a chemokine mediated disease wherein the chemokine binds to one or more chemokine receptors, which comprises administering to a patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 9.

14. A method according to claim 13 in which the chemokine receptor is the CCR4 receptor.

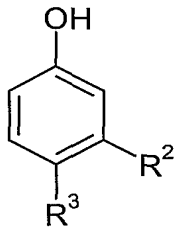
15. A method of treating asthma in a patient suffering from, or at risk of, said disease, which comprises administering to the patient a therapeutically effective amount of a compound of formula (I), or a pharmaceutically acceptable salt thereof, as claimed in any one of claims 1 to 9.

16. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which comprises

(a) reacting a compound of formula (III) wherein R^1 is as defined in formula (I), LG is a leaving group and P^1 is a protecting group with a compound of formula (IV) wherein R^2 and R^3 are as defined in formula (I),

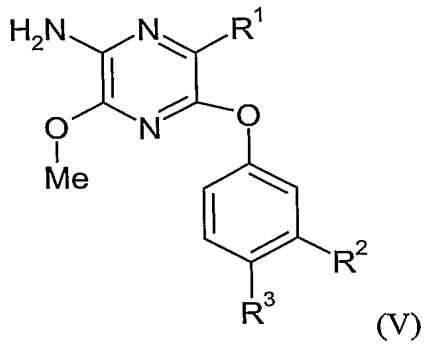


(III),



(IV); or

(b) reacting a compound of formula (V), wherein R^1, R^2 and R^3 are as defined in formula (I) with 2,3-dichlorobenzenesulfonyl chloride,



(V)

and optionally after (a) or (b) carrying out one or more of the following:

- removing any protecting groups
- converting the compound to a further compound of the invention
- forming a pharmaceutically acceptable salt of the compound.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2006/001060

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ, CHEM ABS DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03059893 A1 (ASTRAZENECA AB), 24 July 2003 (24.07.2003), see especially example 73, page 62	1-16
A	WO 03051870 A1 (ASTRAZENECA AB), 26 June 2003 (26.06.2003)	1-16
A	WO 2004108692 A1 (ASTRAZENECA AB), 16 December 2004 (16.12.2004)	1-16
A	EP 1541563 A1 (ONO PHARMACEUTICAL CO., LTD.), 15 June 2005 (15.06.2005)	1-16

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 December 2006	19 -12- 2006
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Renzo C. Verboom/MP Telephone No. +46 8 782 25 00

International patent classification (IPC)

C07D241/22(2006.01)
A61K31/4965(2006.01)
A61P 11/06 (2006.01)

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Use the application number as username.
The password is **TUYALAFLTN.**

Paper copies can be ordered at a cost of 50 SEK per copy from PRV InterPat (telephone number 08-782 28 85).

Cited literature, if any, will be enclosed in paper form.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2006/001060

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 13-15
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 13-15 relate to a method of treatment of the human or animal body by surgery or by therapy, as well as diagnostic

.../...

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

Box II.1

methods /Rule 39.1(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds.

WO	03059893	A1	24/07/2003	AU	2003201802	A	00/00/0000
				BR	0306922	A	09/11/2004
				CA	2472204	A	24/07/2003
				CN	1639132	A	13/07/2005
				DE	10296133	T	15/04/2004
				EP	1467976	A	20/10/2004
				IL	162678	D	00/00/0000
				JP	2005521650	T	21/07/2005
				MX	PA04006806	A	06/12/2004
				NO	20043370	A	28/09/2004
				NZ	533750	A	31/03/2006
				PL	371432	A	13/06/2005
				RU	2004119966	A	10/06/2005
				SE	0200119	D	00/00/0000
				US	20040113409	A	17/06/2004
				US	20060025423	A	02/02/2006
				ZA	200405260	A	03/10/2005
				CA	2463093	A	17/04/2003
				EP	1436058	A	14/07/2004
				JP	2005504972	T	17/02/2005
				SE	0201857	D	00/00/0000
				US	20050029191	A	10/02/2005
WO	03051870	A1	26/06/2003	AT	312096	T	15/12/2005
				AU	2002358390	A	00/00/0000
				DE	60207890	D,T	10/08/2006
				EP	1458715	A,B	22/09/2004
				SE	1458715	T3	
				JP	2005516936	T	09/06/2005
				SE	0104474	D	00/00/0000
				US	20050075346	A	07/04/2005
				AU	2002353717	A	00/00/0000
				BR	0214342	A	14/09/2004
				CA	2466491	A	30/05/2003
				EP	1461327	A	29/09/2004
				IL	160630	D	00/00/0000
				JP	2005509676	T	14/04/2005
				MX	PA04004842	A	02/08/2004
				NO	20042161	A	17/08/2004
				SE	0202139	D	00/00/0000
WO	2004108692	A1	16/12/2004	AU	2003274862	A	11/05/2005
				EP	1633729	A	15/03/2006
				EP	1675695	A	05/07/2006
				SE	0301653	D	00/00/0000
				US	20060122195	A	08/06/2006
				WO	2005039799	A	06/05/2005
EP	1541563	A1	15/06/2005	AU	2003252478	A	02/02/2004
				US	20060004010	A	05/01/2006
				WO	2004007472	A	22/01/2004